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## Prevention of falling in older persons with a high risk of recurrent falling

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Welkom in mijn proefschrift

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## **General Introduction**

Deelnemer onderzoek (80 jaar): "Men haalt meer kennis uit het verleden dan uit de toekomst."

## General Introduction

As we grow older, the number of health challenges increase. In old age, there are more chronic diseases to deal with, the physical and cognitive capacities decline, and recovery is often incomplete. Consequently, physical functioning decreases and the need for care increases. Falling is often a first sign of physical decline and also a risk factor for further decline and future falls.<sup>1</sup> Unfortunately, measures to prevent falls are not very (cost-)effective in unselected populations.<sup>2</sup> This thesis discusses the problem of falling in old age from various perspectives. In this introductory chapter, the context and outline of this thesis will be sketched.

## The aging society

The number of persons of 65 years and older in the Netherlands increased from 2.15 million in 2000 to 2.41 million in 2008 (12 % raise) and is expected to continue to rise to 3.28 million in 2020.<sup>3</sup> The increase in number of persons of 80 years and older is even stronger: from 500,339 in 2000 to 615,489 in 2008 (23 % raise).<sup>3</sup> Not only the number of older persons has increased, also the prevalence of chronic diseases is larger than before. Between 2001 and 2008, the prevalence of five of the seven major chronic diseases increased among 65+-year olds (i.e. cardiac diseases, chronic non-specific lung diseases, diabetes mellitus, stroke and malignant diseases).<sup>3</sup> Of the 55-64 year olds, in 1992/93 29 % had 2 or more chronic diseases, whereas in 2002/03 41 % had 2 or more chronic diseases.<sup>4</sup> These statistics illustrate that both the number of older persons and the average number of chronic diseases per person have risen in the past decade and are expected to continue to rise in the next decade.

## Falling in old age

Falling is a major health problem in old age. Annually, about 30 % of the community-dwelling persons of 65 years and older falls once and 15 % falls twice or more.<sup>5,6</sup> The consequences of falling can be severe: 68 % reports a physical injury, 6 % suffers a major injury (such as hip fracture) and 29-92 % reports fear of falling.<sup>7-9</sup> Subsequently, a fall can lead to decreased physical functioning, loss of independence, nursing home admittance, and even death.<sup>5,8,10,11</sup> The high incidence and severe consequences emphasize the need for preventive measures.

### *Definition of (recurrent) falling*

A fall is defined as “an unintentional change in position resulting in coming to rest on the ground or other lower level”.<sup>12</sup> In the literature, a distinction is made between once-fallers and recurrent fallers. Falling refers to any fall and includes occasional falls. Occasional falls may be caused mainly by extrinsic factors, (i.e. environmental factors that act upon the person), whereas recurrent falls are usually caused by intrinsic factors (i.e. physical, cognitive and behavioural factors within the person, e.g. mobility limitations and cognitive decline). We defined recurrent falling as two or more falls within 6 months.<sup>13</sup>



**Table 1.** Risk factors for falling and recurrent falling in independently living older persons

<b>Risk factor</b>	<b>Falling</b>	<b>Recurrent falling</b>
Age	20, 21	
Chronic diseases	14,20,21	22
Cognitive impairments	5,21	23
Depressive symptoms	21,25	24
Dizziness	15,21	26,27
Fall history	21,28,29	24,26,27,28,30
Fear of falling		26,27
High levels of physical activity	15,17	
Low levels of physical activity	14,16,18	16
Limitations in daily activities	29	26,28
Mobility problems	5,14,15,21,29	22,24,30
Muscle weakness	14	24,26
Orthostatic hypotension	31	27
Urinary incontinence	21,28	27,28
Use of psychotropic medication	5,14,20,28	30
Vision impairments	21,28	28,32

The numbers refer to the articles in the reference list that reported these risk factors.

### *Risk factors*

Many epidemiological studies have identified risk factors for falling and recurrent falling. Table 1 provides an overview of risk factors for falling and recurrent falling in independently living older persons. In the literature, both low and high levels of physical activity have been associated with falling.<sup>14-18</sup> This has led to the hypothesis that there may be a U-shaped relationship between physical activity and fall risk.<sup>19</sup> If this is true, physical activity advices given by the public authorities, for example to decrease cardiovascular diseases, may increase the level of activity and thereby the number of falls. However, this hypothesis has not been tested yet.

### *Screening of fall risk*

In 2004, the guideline “Prevention of falling in older persons” was released by the Dutch Institute for Healthcare Improvement (CBO).<sup>33</sup> This guideline recommends screening older persons for fall risk factors and providing subsequent interventions to decrease the fall risk. By selecting persons at high risk of falling the (cost-)effectiveness of preventive measures may be improved.<sup>33-35</sup> Prediction models can be used to identify older persons with a high risk of falling. Several prediction models have been developed, but none have been validated in an independent, clinically relevant sample.

One of the existing prediction models has been developed in the Longitudinal Aging Study Amsterdam (LASA). LASA is an ongoing multidisciplinary cohort study on predictors and consequences of changes in physical, cognitive, emotional and social functioning in older

persons in the Netherlands.<sup>36,37</sup> A subsample of 1365 participants aged 65 years and older who were living in the community reported falls between 1995/96 and 1998/99. Predictors estimate the probability of a future event. Predictors can be both risk factors and risk indicators. In case of a risk factor, there is a causal relationship between a determinant and the outcome measure. Risk indicators, on the other hand, do not have a causal relationship with the outcome measure, but can co-exist with the outcome measure and therefore be an appropriate predictor. For example, both dizziness and having a dog or cat in the household are predictors of falling. Dizziness is a risk factor (dizziness can cause postural instability and therefore an increased fall risk), while having a dog is a risk indicator (dog owners may stumble over the leash while taking the dog for a walk, the presence of the dog itself, however, does not directly cause a fall). Table 2 shows the predictors that were selected as the optimal set to predict recurrent falling.<sup>26</sup> The discriminative ability of this risk profile was 0.71, indicating that 71 % of the participants were correctly classified as recurrent faller or non-recurrent faller. However, the accuracy of prediction models is usually higher in the original sample than in the general population (optimism).<sup>38</sup> Furthermore, the fall risk profile was developed in a general population of community-dwelling older persons but it is practically not feasible to screen every older person. If the risk profile is used in clinical settings to screen which persons have the highest fall risk and are most in need of preventive measures, it is important to evaluate how accurate the fall risk profile predicts the risk of recurrent falling in a group of older persons who consult a family physician or Emergency department after a fall.

**Table 2.** Predictors included in the LASA fall risk profile

Predictor	Weighted scores
≥2 falls in the previous year	4
Dizziness	4
Functional limitations (>2)	3
Grip strength (women≤32 kg, men≤56 kg)	3
Body weight (women≤62 kg, men≤70 kg)	2
Fear of falling (FES≥1)	2
Dogs or cats in the household	2
Education (≥11 years)	1
Alcohol use (≥15 consumptions per week)	1
Alcohol use x Education	4
≥Two falls in previous year x Fear of falling	4

Adapted from SMF Pluijm et al. 2006, *Osteoporosis Int*, 17, 417-425.

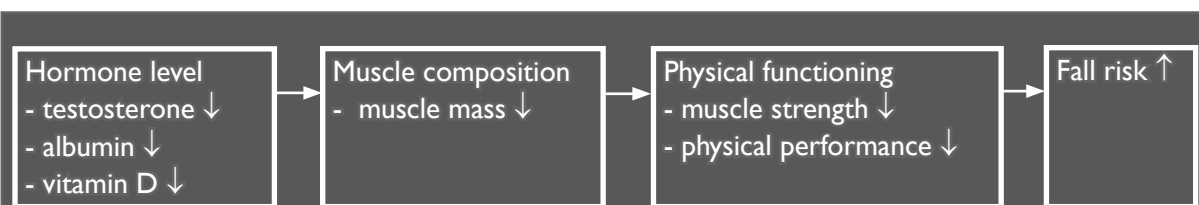
Per predictor, points are scored and the scores are summed (range 0-30). Higher scores indicate higher risks of recurrent falling. For example, an 80 year old lady who fell 3 times in the preceding year, who owns a cat and who is very afraid to fall again would score 4 (≥2 falls in previous year) + 2 (fear of falling) + 2 (cat) + 4 (≥2 falls in previous year in combination with fear of falling) = 12 points. Depending on the cut-off score used, this lady would have a high (cut-off scores≤12) or low (cut-off scores≥13) risk of recurrent falling.

*The cost-effectiveness of preventive measures*

Since 1990, many trials have studied the effectiveness of fall prevention programs. The programs can be divided into single interventions (e.g. strength and balance exercises, revision of medication and home hazard reduction) and multifactorial interventions (including a multidisciplinary evaluation and subsequently an individually tailored treatment of risk factors). Meta-analyses suggest that multifactorial interventions may be effective in unselected populations, but evidence of effectiveness in high-risk populations is lacking.<sup>2,39,40</sup> Only two studies have evaluated the cost-effectiveness of multifactorial interventions.<sup>35,41</sup> However, the results of these studies are conflicting and no conclusive evidence is available that the screening and targeted treatment of risk factors is cost-effective compared to usual care.

**Cortisol, muscle composition, physical functioning, and fall risk**

Sarcopenia is known as the age related decline in muscle mass and muscle strength.<sup>42</sup> Loss of muscle strength is a risk factor for loss of physical function, and both muscle weakness and poor physical function are risk factors for falling.<sup>43,44</sup> The declines in muscle parameters have been associated with age-related hormonal changes and poor nutritional status, such as a decrease in serum 25-hydroxyvitamin D, serum albumin, and testosterone.<sup>45-48</sup> These hormonal changes have also been associated with poor physical functioning and falling.<sup>45,49-51</sup> Figure 1 presents the relative context of these associations. An other hormone that may add to the explanation of the variance in physical functioning and fall risk is cortisol. High levels of cortisol, as occurs in Cushing's syndrome or glucocorticoid therapy, have been associated with muscle weakness.<sup>52,53</sup> Also, genetic variations in the glucocorticoid receptor gene, which decrease the effect of cortisol on target tissues, have been associated with beneficial body composition and muscle strength in healthy young adults.<sup>54</sup> Whether variations in cortisol levels within the normal range are associated with muscle composition, physical functioning or fall risk has not been studied yet among older adults.



**Figure 1.** The potential pathway from hormone level to fall risk

*Cortisol and the glucocorticoid receptor*

The glucocorticoids consist for the major part of cortisol.<sup>55</sup> Cortisol is known as the stress hormone and in case of stress it exerts many effects including metabolic, cardiovascular, respiratory, renal and immune responses to re-establish homeostasis.<sup>55</sup> The circadian rhythm of the cortisol level is characterised by a peak in the morning and a trough level in the evening, which represent peak and basal secretion, respectively. In addition, cortisol levels fluctuate during the day and with stress.<sup>56-58</sup> In response to stress, the serum level of cortisol increases and after initiation of the various responses, the basal level is restored via its negative feedback mechanism.<sup>55</sup> In old age, the basal level, i.e. the evening level, increases.<sup>57,59-61</sup> Although of vital importance, sustained high levels of cortisol may have negative effects.

A Single Nucleotide Polymorphism (SNP) is defined as a variation in the DNA of one single nucleotide. At one specific position in the human genome, different nucleotides can be found (for example AAGGTTA → AAGGCTA). These variations may affect the function, functionality or the production of the proteins.<sup>62</sup> Similarly, the effects of cortisol on target tissues are mediated by variations of the glucocorticoid receptor (GR).<sup>63</sup> In the literature, four SNPs of the GR gene have been described which alter the sensitivity to cortisol: N363S, *Bcl1*, ER22/23EK, and 9β. The N363S and *Bcl1* polymorphisms have been associated with increased sensitivity to cortisol,<sup>64,65</sup> whereas the ER22/23EK and 9β polymorphisms have been associated with decreased sensitivity to cortisol.<sup>66,67</sup> Increased sensitivity means that the impact of a certain amount of cortisol on its target tissue is greater in carriers (those who have the polymorphism) than in non-carriers (wild-type). Associations of these polymorphisms have been found with changes in body composition, bone mineral density, coronary artery disease and muscle strength.<sup>54,65,68,69</sup> Thus, GR gene polymorphisms may modify the relationships between cortisol and other physical outcome measures.

*The role of cortisol in chronic diseases*

An alternative pathway for the relationship between cortisol and falling may be via chronic diseases. Presence of chronic diseases is an independent risk factor for falling, but also affects other risk factors for falling, such as physical activity, mobility and orthostatic hypotension. In the literature, associations between high levels of cortisol and increased risk of cardiovascular disease, diabetes mellitus and stroke have been found.<sup>68,70,71</sup> Furthermore, the associations between cortisol and chronic diseases may be different in diseases with inflammatory episodes such as COPD and rheumatoid arthritis. In these diseases, corticosteroids are often prescribed to suppress inflammation. Accordingly, endogenous high levels of cortisol may protect against COPD and rheumatoid arthritis. Since cortisol levels gradually increase with aging, it is interesting to examine whether endogenous levels of cortisol are associated with age-related chronic diseases in a general older population.

## **The outline of this thesis**

The main objective of this thesis is prevention of falling in older persons with a high risk of recurrent falling. In the Chapters 2 to 4, the relationship between cortisol and several risk factors for falling will be studied. The relationship between cortisol and physical performance is studied in Chapter 2. Cortisol may affect physical performance via muscular atrophy. The relationship between cortisol and muscle parameters and the role of variations in the glucocorticoid receptor gene in these relationships are studied in Chapter 3. Whether endogenous levels of cortisol in a general older population are associated with mortality and chronic diseases such as chronic non-specific lung disease and joint diseases is examined in Chapter 4.

In the literature, both high and low levels of physical activity have been found to be associated with an increased fall risk and a U-shaped relationship has been hypothesized.<sup>15,19</sup> In Chapter 5, this hypothesis is tested. Although several prediction models for fall risk have been developed, none of these models have been validated in independent, clinically relevant samples. In Chapter 7, the fall risk profile that was developed in the LASA study is validated in a new sample of older persons who visited the Emergency department or their family physician after a fall.

Chapter 6 describes the design of a randomized controlled trial to study the cost-effectiveness of a multifactorial intervention (which follows the CBO-guideline) to prevent falling in older persons with a high risk of recurrent falling. The effectiveness and cost-effectiveness of this trial are studied in Chapters 8 and 9. Chapter 10 discusses the findings presented in Chapters 2 to 9.

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# 2

## **Relationship between cortisol and physical performance in older persons**

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Potentiële deelnemer (80 jaar): “Ik weet niet of ik geschikt ben voor uw onderzoek, want ik ben gevallen toen ik tijdens het hardlopen over een hekje wilde springen. Ik dacht dat ik nog jong was.”

## Abstract

**Objective** Hypercortisolism is associated with muscle weakness. This study examines the relationship between cortisol and physical performance in older persons.

**Methods** The study was conducted within the Longitudinal Aging Study Amsterdam (LASA), an ongoing cohort study in a population-based sample of healthy older persons in the Netherlands. Data from the second (1995/1996) and fourth (2001/2002) cycle were used containing 1172 (65-88 years) and 884 (65-94 years) men and women, respectively. Physical performance was measured by summing the scores on the chair stands, tandem stand and walk test (range 0-12). In the second cycle serum total and free cortisol were assessed; in the fourth cycle evening salivary cortisol was assessed. Regression analysis (stratified for sex, adjusted for age, body mass index, alcohol use, physical activity and region) was conducted to examine the cross-sectional relationship between cortisol and physical performance.

**Results** Women with higher serum free cortisol scored more poorly on physical performance ( $b=-0.28$  per SD higher cortisol,  $p=0.016$ ), which was mainly explained by poorer performance on the tandem stand ( $OR=1.32$  for a lower score per SD higher cortisol,  $p=0.003$ ). Men with higher salivary cortisol scored more poorly on physical performance ( $b=-0.90$  in the highest versus the lowest quartile,  $p=0.008$ ), which was mainly explained by poorer performance on the chair stands and walk test ( $OR=1.88$ ,  $p=0.020$  and  $OR=1.81$ ,  $p=0.027$ , respectively, in the highest versus the lowest quartile).

**Conclusion** Physical performance is negatively associated with high cortisol levels in older persons.

**Introduction**

Cortisol is known to stimulate degradation and inhibit synthesis of muscle proteins.<sup>1,2</sup> Hypercortisolism, as occurs in Cushing's syndrome or glucocorticoid therapy, is associated with muscle atrophy and weakness.<sup>3,4</sup> One study found that variations in serum cortisol within the normal range are negatively related to muscle strength of the knee extensors.<sup>5</sup> However, it is not known whether similar associations exist between cortisol and physical performance, including strength, balance, and coordination in the lower extremities.

During aging, muscle tissue is gradually lost, contributing to reduced muscle strength.<sup>6,7</sup> Loss of muscle strength is associated with loss of physical function, which may lead to falls, fractures, loss of independence, and nursing home admission.<sup>8-10</sup> Age-related hormonal changes, including cortisol, may partly cause these muscular changes.<sup>1,2,6,11</sup> Several studies have investigated the relationship between aging and cortisol. Although there are conflicting results, the majority of the studies measuring morning or 24-hour plasma cortisol concentrations in large samples show that basal cortisol levels increase with age.<sup>12-14</sup> Furthermore, in older persons, both morning and 24-hour plasma cortisol levels are higher in women than in men.<sup>12,13,15</sup>

To our knowledge, the relationship between cortisol and physical performance has not been investigated. This study examines the relationship between cortisol and physical performance in older persons. It is hypothesized that high cortisol levels are associated with poorer physical performance. The results of this study add to the understanding of mechanisms in aging that influence physical functioning.

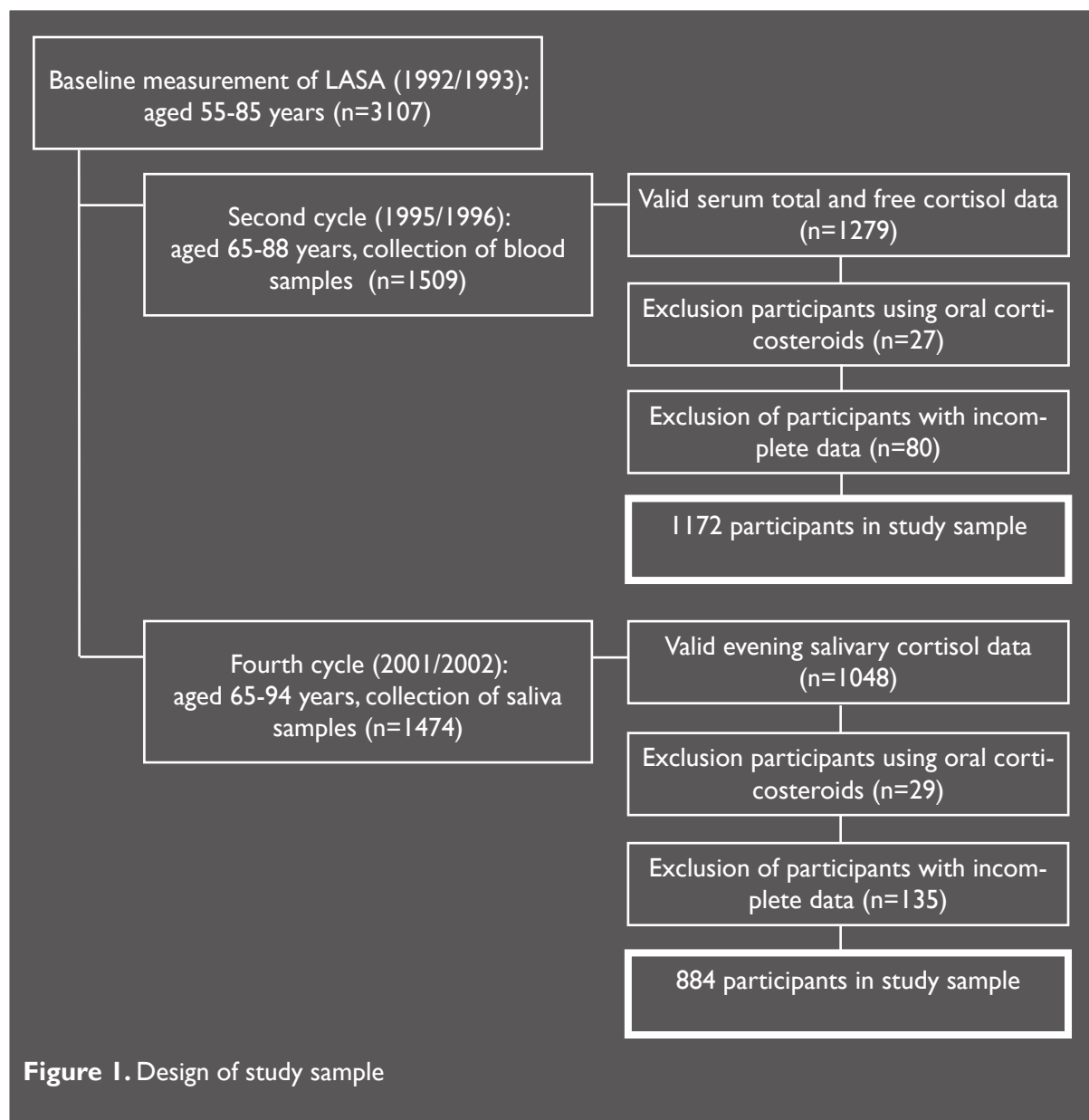
**Methods***Subjects*

The study was performed within the Longitudinal Aging Study Amsterdam (LASA), an ongoing interdisciplinary cohort study on predictors and consequences of changes in physical, cognitive, emotional and social functioning in older persons.<sup>16</sup> A random sample of older men and women stratified for age, sex and expected five years mortality rate was drawn from the population registry of eleven municipalities in areas in the west, northeast and south of the Netherlands. The sample is representative for the older Dutch population with respect to geographic region and degree of urbanization. The sampling and data collection procedures have been described in detail elsewhere.<sup>17</sup> The sample for this study consisted of participants who took part in the main and medical interview of the second (1995/1996) and/or fourth cycle (2001/2002) of LASA. The design of the study sample is presented in Figure 1. The Medical Ethics Committee approved the study and all participants signed informed consent.

## Relationship between cortisol and physical performance

Second cycle: Participants who were born before 1930 (aged 65 and older as of January 1, 1996) and of whom a valid serum cortisol value was obtained were included (n=1279). Participants using oral corticosteroids (n=27) or having an incomplete dataset (n=80) were excluded. The total number of participants included in the serum cortisol analysis was 1172. These respondents were significantly younger, drank more alcohol, had less chronic diseases, were more often able to walk and more often lived in Amsterdam or vicinity compared to excluded respondents.

Fourth cycle: Participants who were born before 1936 (aged 65 and older as of January 1, 2002) and of whom valid salivary cortisol values were obtained were included (n=1048). Five participants had cortisol levels over 100 nmol/L. These extreme levels were considered to be outliers and were excluded. Participants using oral corticosteroids (n=29) or having an incomplete dataset (n=135) were excluded. The total number of participants included in the salivary cortisol analysis is 884.



**Figure 1.** Design of study sample

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These respondents were significantly younger, took more alcohol, had less chronic diseases, were less depressed, were more often able to walk (without walking aids) and were more physically active compared to excluded respondents. In total, 499 participants took part in both cycles (42 % of the second and 56 % of the fourth cycle). Therefore, the samples are partly dependent.

### *Measurements*

In the second cycle cortisol was determined in serum, whereas in the fourth cycle, cortisol was measured in saliva. All other variables, including physical performance, were assessed using identical methodology and equipment in all cycles.

### *Serum total cortisol, corticosteroid binding globulin and serum free cortisol*

Participants were invited to a health care center near their homes where blood samples were collected in the morning; participants were allowed to take tea and toast before, but no dairy products. Although the exact time of blood collection was not recorded, most participants had their blood samples taken before 10 AM. The blood samples were centrifuged and serum was stored at  $-70^{\circ}\text{C}$  until processing in 2002/2003. The serum levels of cortisol were determined in singlicate using a competitive immunoassay (ACS: centauer, Bayer Diagnostics, the Netherlands). The lower limit for accurate detection of cortisol was 30 nmol/l and the inter-assay coefficients of variation (CV) were 6 % at 150 nmol/l and 8 % at 1000 nmol/l.

Corticosteroid binding globulin (CBG) levels were determined using a radio-immunoassay (Medgenix Diagnostics, Belgium) method independent of serum total cortisol. The lower limit for accurate detection of CBG concentrations was 11 mg/l and the inter-assay CV's were 8 % at 30 mg/l and 5 % at 110 mg/l. In none of the samples the concentrations of cortisol or CBG fell below the lower detection limits. Serum free cortisol was computed according to the Free Cortisol Index: serum total cortisol (nmol/l) divided by CBG (mg/l).<sup>18</sup>

### *Evening salivary cortisol*

Saliva samples were collected using cotton balls. Participants were asked to rinse their mouth with water and wait ten minutes before starting to chew the cotton ball. They had to prevent bleeding of the gum previous to and during the collection of the saliva. The cotton balls were chewed on around 23.00h for approximately 1.5 minutes and then put in a tube. The samples were kept refrigerated until processing. Radio Immunoassay coated tubes (Spectria Orion Diagnostics, Finland) were used to determine evening salivary cortisol (in duplicate). The lower limit for accurate detection was 1.5 nmol/l. None of the measured salivary cortisol concentrations fell below the lower detection limit. The intra- and inter-assay coefficients of variation (CV) were less than 19 %.

### *Physical performance*

Three standardized performance tests were conducted: chair stands, tandem stand and walk test. The chair stands mainly measures proximal leg strength and the tandem stand mainly measures balance. The walk test mainly measures proximal leg strength, balance, and coordination. During the chair stands test the participant stands up from a chair and sits down for five consecutive times as fast as possible with the arms folded. The walk test is a test in which the participant walks 3 meters along a line, turns 180° and walks back as fast as possible without running. During the tandem stand test the participant stands with one foot behind the other (heel against toe) for 10 seconds. The scores of the chair stands and walk test range from 1 (slowest) to 4 (fastest), corresponding to the quartiles of time required in the total population at baseline. The score of 0 was assigned when the participant was unable to complete the test. For the tandem stand, 0 points were assigned when the participant was unable to perform the test, 2 points when able to hold for 3 to 9 seconds, and 4 points when able to hold for 10 seconds or more. Physical performance was computed by summing the scores on the three tests (range 0-12) and a high score indicates a good performance.<sup>19</sup> In large cohort studies, this score has been a valid measure for physical functioning. It is associated with disability, the onset of disability and other health-related factors in older persons.<sup>20-22</sup>

### *Potential effect modifiers*

Gender was derived from the municipal registries. Gender differences have been reported in both the basal activity of the hypothalamic-pituitary-adrenal (HPA) axis<sup>13</sup> and the response of the HPA-axis to challenge.<sup>23</sup> Furthermore, other hormones are known to have different effects in women and men. Similarly, cortisol may have a different effect in women and men. Therefore, gender was considered as a potential effect modifier in the relationship between cortisol and physical performance.

### *Potential confounders*

Age was derived from the municipal registries. Region was assessed as living in the west (Amsterdam and vicinity), north-east (Zwolle and vicinity) or south (Oss and vicinity) of the Netherlands. Body weight was measured without upper clothes and shoes using a calibrated balance beam scale. Body height was measured using a stadiometer. Body weight and height were used to compute the body mass index ( $BMI = \text{mass (kg)} / \text{length (m)}^2$ ). Alcohol consumption (drinking alcohol, 0 vs. 1-14 vs. 15 glasses or more per week), smoking (current smoker, yes/no), use of a walking aid (yes/no), dizziness (yes/no), and hypertension (yes/no) were assessed. The presence of chronic diseases was assessed with a questionnaire on self-reported chronic diseases, which included chronic obstructive pulmonary disease (COPD), cardiac diseases, vascular diseases, stroke, diabetes mellitus, malignant neoplasms and joint disorders (i.e. osteoarthritis and rheumatoid arthritis). The number of present chronic diseases was counted (range 0-7).



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Depressive symptoms were assessed using the Center for Epidemiologic Studies-Depression scale (CES-D). The CES-D is a 20-item self-report scale designed to measure depressive symptoms in the community. The score ranges from 0-60 and a score of 16 and higher was interpreted as the presence of clinically relevant depressive symptoms.<sup>24</sup> Medication use was assessed by recording the medications of the participant directly from the containers. Level of physical activity was measured with the LASA physical activity questionnaire (LAPAQ).<sup>25</sup> The LAPAQ is an interviewer-mediated questionnaire in which the frequency and duration of participation is estimated in six activities during the previous two weeks. The activities are walking, cycling, light and heavy household work, and first and second sport. The number of minutes participated in each of the activities per day were summed up to a physical activity score. Because renal function and liver function may influence cortisol metabolism, creatinine (n=1172) and gamma GT (n=353, only measured in Zwolle and vicinity) were determined in the second cycle using routine laboratory methods; coefficients of variation were 3 % and 1.2 %, respectively.

### *Statistical analysis*

All analyses were conducted using SPSS software (version 12.0.1). To examine the relationship between any of the cortisol measures and physical performance five steps were performed in the analyses. First, the independent variables were tested for linearity. Both serum total and serum free cortisol were linearly related to the outcome and therefore included continuously. Evening salivary cortisol was not linearly related to physical performance and therefore included in quartiles. Cut-off points for quartiles were 2.3, 3.0, and 4.3 nmol/l, both in women and men. To improve the comparability between the models, serum total and serum free cortisol were also studied in quartiles. Cut-off points for serum total cortisol quartiles were 355, 453, and 585 nmol/l in women and 407, 498, and 617 nmol/l in men. Cut-off points for serum free cortisol quartiles were 7.88, 10.14, and 13.50 in women and 10.75, 16.53, and 16.84 in men. The variables BMI and level of physical activity were not linearly related to physical performance. Therefore, BMI was included in quartiles and physical activity was included in sixtiles (which modeled the non-linear pattern of the relationship more adequately than quartiles). Second, it was tested whether the interaction with gender was significant ( $p < 0.10$ ). Third, simple linear regression was conducted. Fourth, multiple linear regression was performed with adjustment for those confounders which led to a change in the regression coefficient of the association between cortisol and performance of more than 10 %. This was the case when age, alcohol use, physical activity, BMI, and region were added to the model (in all cortisol measures). Fifth, to test which of the individual performance tests had the strongest relationship with cortisol, cumulative logistic ordinal regression was used which has the feature of proportional odds (SPSS, PLUM).<sup>26,27</sup> P-values were based on two-sided tests and were considered statistically significant at  $p < 0.05$ .

## Results

In the second cycle, 600 women and 572 men were included with mean serum total cortisol concentrations of 480.0 nmol/l (Standard Deviation=173.4) and 517.8 nmol/l (SD=161.4) and mean serum free cortisol concentrations of 10.9 (SD=4.1) and 14.0 (SD=4.4), respectively. In the fourth cycle, 464 women and 420 men were included. The median evening salivary cortisol concentration was 3.0 nmol/l (Interquartile Range=[1.2-4.8]) in women and 3.0 nmol/l (IQR=[1.0-5.0]) in men. Table 1 shows the characteristics of the participants in both cycles. Figure 2 shows that, over the full range of serum free cortisol values measured, physical performance decreased with more than 2 points in women.

In the second cycle, an interaction with gender was found for serum free cortisol ( $p=0.001$ ) but not for serum total cortisol ( $p=0.13$ ). To enhance the comparability, all models were analyzed for men and women separately. In women, an unadjusted relationship was found between both

**Table 1.** Baseline data for men and women in the second and fourth cycle

	Second cycle		Fourth cycle	
	Women (n=600)	Men (n=572)	Women (n=464)	Men (n=420)
Age	75.1 (6.4)	75.3 (6.5)	75.1 (6.7)	75.1 (6.8)
Body Mass Index	27.4 (4.7)	26.1 (3.3)	27.8 (4.7)	26.7 (3.3)
Alcohol (% $\geq 15$ glasses/week)	11.0	31.1	12.5	29.4
Smoking (% yes)	12.5	24.1	9.9	20.5
Number of chronic diseases	1.2 (1.1)	1.2 (1.1)	1.4 (1.0)	1.3 (1.1)
Depression (% CES-D $>16$ )	20.3	7.2	16.6	9.9
Use of walking aid (% yes)	3.8	2.3	2.9	1.4
Physical activity (min/day) <sup>‡</sup>	163.7 [110.1-222.9]	106.4 [60.0-171.6]	161.3 [108.4-229.8]	107.0 [65.6-168.8]
Region (% Amsterdam)	47.0	46.7	43.7	43.4
Walk test <sup>‡</sup>	2.0 [1.0-3.8]	3.0 [2.0-4.0]	2.0 [1.0-3.0]	2.0 [1.3-4.0]
Chair stands	1.9 (1.2)	2.3 (1.1)	2.1 (1.1)	2.3 (1.1)
Tandem stand (% able $\geq 10$ s)	61.0	72.7	70.2	80.7
Physical performance	7.0 (3.2)	8.1 (2.8)	7.4 (3.0)	8.1 (2.7)
Serum total cortisol	480.0 (173.4)	517.8 (161.4)	-	-
CBG <sup>##</sup>	43.8 [39.1-50.0]	36.5 [33.0-41.0]	-	-
Serum free cortisol <sup>#</sup>	10.9 (4.1)	14.0 (4.4)	-	-
Evening salivary cortisol <sup>†‡</sup>	-	-	3.1 [2.3-4.1]	3.0 [2.3-4.3]

All variables are presented in mean (standard deviation) unless stated otherwise. <sup>‡</sup> Results are presented in median [interquartile range]. <sup>#</sup> Serum free cortisol=serum total cortisol (nmol/l)/CBG (mg/l); nmol/l=27.5 $\mu$ g/dl. <sup>†</sup> Salivary cortisol is presented in nmol/l.

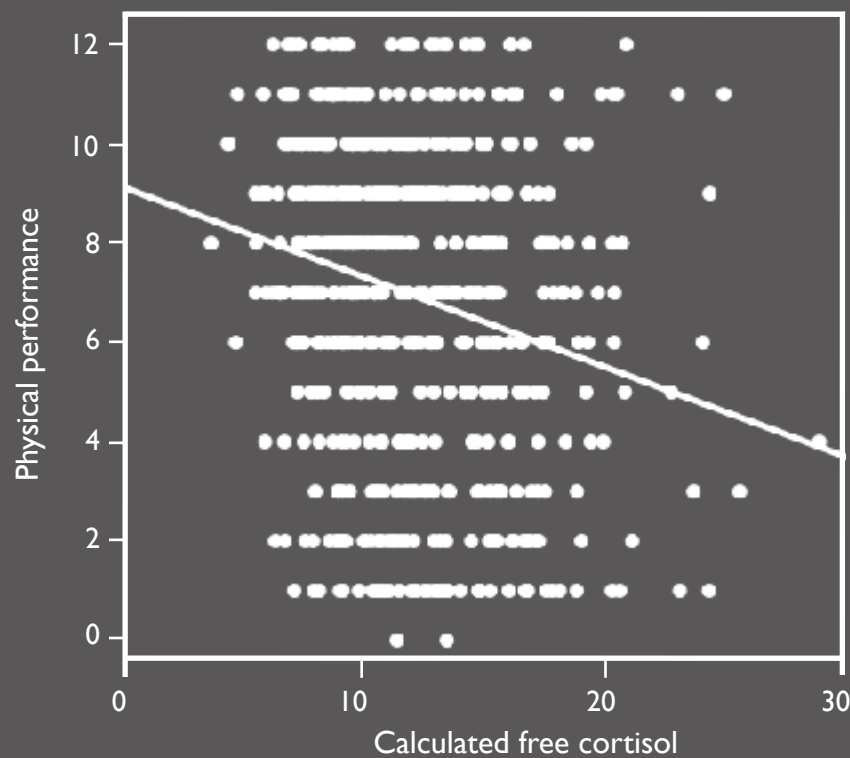


Figure 2. Relationship between calculated free cortisol and physical performance in women  
This graph shows the scatter plot of the continuous data and unadjusted regression line for the relationship between calculated free cortisol (x-axis) and physical performance (y-axis) in women.

serum total and serum free cortisol and physical performance (Table 2). After adjustment, only the relationship between serum free cortisol (both continuously and in quartiles) and physical performance remained significant. One SD higher serum free cortisol level (continuous) was associated with a poorer physical performance score of 0.28 points ( $r^2=0.35$ ). The most important confounders were age and alcohol use (range 0-2) with regression coefficients of  $-0.21$  points per year and  $0.60$  points per category, respectively. Women in the highest quartile of serum free cortisol had  $0.88$  points poorer physical performance score as compared with those in the lowest quartile. In men, no significant relationships were found after adjustment for confounding.

In women, ordinal regression showed that there was a relationship between both serum total and serum free cortisol (continuous) and the tandem stand (Table 3). These relationships remained significant after adjustment for confounding. The cumulative odds for a lower score on the tandem stand test became  $1.28$  times as large when serum total cortisol increased with one SD and  $1.32$  times as large when serum free cortisol increased with one SD. Furthermore, a relationship was found between serum free cortisol and the chair stands and walk test, respectively. However, after adjustment for confounding, the latter associations were no longer statistically significant. No significant relationships were found in men between serum total or

## Relationship between cortisol and physical performance

**Table 2.** Relationship between serum cortisol and physical performance

		Women		Men	
		regression coefficients	p-value	regression coefficients	p-value
serum total cortisol <sup>#</sup>		-0.39	0.002	-0.11	0.36
serum total cortisol (adjusted) <sup>#†</sup>		-0.17	0.13	-0.05	0.64
serum free cortisol <sup>#</sup>		-0.69	<0.001	-0.14	0.23
serum free cortisol (adjusted) <sup>#†</sup>		-0.28	0.02	0.09	0.43
serum total cortisol	Q1	0		0	
	Q2	-0.35	0.34	-0.59	0.08
	Q3	-0.53	0.14	-0.57	0.09
	Q4	-1.25	0.001	-0.54	0.10
serum total cortisol (adjusted) <sup>†</sup>	Q1	0		0	
	Q2	-0.20	0.51	-0.37	0.23
	Q3	-0.20	0.52	-0.16	0.60
	Q4	-0.61	0.05	-0.41	0.19
serum free cortisol	Q1	0			
	Q2	-1.08	0.003	-0.69	0.04
	Q3	-1.40	<0.001	-0.19	0.57
	Q4	-1.98	<0.001	-0.78	0.02
serum free cortisol (adjusted) <sup>†</sup>	Q1	0		0	
	Q2	-0.49	0.11	-0.34	0.27
	Q3	-0.38	0.23	0.19	0.55
	Q4	-0.88	0.007	-0.01	0.96

Unstandardized regression coefficients are presented for the relationship between serum cortisol and physical performance: with serum cortisol continuously (<sup>#</sup> expressed per SD higher serum cortisol: women  $SD_{\text{total cortisol}} = 173.4 \text{ nmol/l}$ ,  $SD_{\text{free cortisol}} = 4.1$ , men  $SD_{\text{total cortisol}} = 161.4 \text{ nmol/l}$ ,  $SD_{\text{free cortisol}} = 4.4$ ) and in quartiles (the lowest quartile being the reference quartile). <sup>†</sup> Adjusted for age, alcohol use, body mass index, physical activity, and region.

serum free cortisol and any of the physical performance tests. The results were similar when serum total and serum free cortisol were included in quartiles (data not shown).

In the fourth cycle, no interaction with gender was found ( $p=0.70$ ). Though, to enhance the comparability, results are presented for men and women separately. Both unadjusted and adjusted relationships between evening salivary cortisol and physical performance were found in women as well as in men (Table 4). Women and men in the highest quartile of salivary cortisol had 0.79 and 0.90 points poorer physical performance scores, respectively, as compared with the lowest quartiles. The most important confounders in women were age and alcohol use (range 0-2), with regression coefficients of  $-0.17$  points per year and  $0.70$  points per category, respectively. In men, the most important confounder was age, with a regression coefficient of  $-0.16$  points per year.

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Ordinal regression showed that there was a relationship between evening salivary cortisol and each of the physical performance tests, both in women and men (Table 5). After adjustment, the relationships with tandem stand were significant in women. Women in the highest quartile had 2.42 times higher odds for a poorer score on the tandem stand as compared with women in the lowest quartile. In men, on the other hand, the relationships between salivary cortisol and both the chair stands and walk test remained significant after adjustment. Men in the highest quartile of salivary cortisol had 1.88 and 1.81 times higher odds for a poorer score on the chair stands and walk test, respectively, as compared with men in the lowest quartile.

**Table 3.** Relationship between continuous serum cortisol and the individual performance tests

	Tandem stand		Walk test		Chair stands	
	OR	p-value	OR	p-value	OR	p-value
<b>Women</b>						
serum total cortisol	1.47	<0.001	1.11	0.16	1.04	0.63
serum total cortisol (adjusted) <sup>†</sup>	1.28	0.007	1.05	0.54	1.04	0.63
serum free cortisol	1.67	<0.001	1.26	0.002	1.25	0.008
serum free cortisol (adjusted) <sup>†</sup>	1.32	0.003	1.09	0.33	1.05	0.52
<b>Men</b>						
serum total cortisol	1.12	0.20	1.05	0.54	0.98	0.79
serum total cortisol (adjusted) <sup>†</sup>	1.04	0.67	1.11	0.19	1.01	0.95
serum free cortisol	1.16	0.12	1.08	0.30	0.97	0.73
serum free cortisol (adjusted) <sup>†</sup>	1.02	0.86	1.01	0.86	1.08	0.31

Odds ratios (OR) for a poorer test result are expressed per SD higher serum cortisol: women  $SD_{\text{total cortisol}} = 173.4 \text{ nmol/l}$ ,  $SD_{\text{free cortisol}} = 4.1$ , men  $SD_{\text{total cortisol}} = 161.4 \text{ nmol/l}$ ,  $SD_{\text{free cortisol}} = 4.4$  and in quartiles (the lowest quartile being the reference quartile). <sup>†</sup> Adjusted for age, alcohol use, body mass index, physical activity and region.

**Table 4.** Relationship between evening salivary cortisol and physical performance

		Women		Men	
		regression coefficients	p-value	regression coefficient	p-value
evening salivary cortisol	Q1	0		0	
	Q2	-0.36	0.37	-1.10	0.003
	Q3	0.23	0.56	-0.74	0.05
	Q4	-1.23	0.001	-1.40	<0.001
evening salivary cortisol (adjusted) <sup>†</sup>	Q1	0		0	
	Q2	-0.39	0.25	-0.79	0.02
	Q3	0.37	0.27	-0.48	0.15
	Q4	-0.79	0.03	-0.90	0.008

Unstandardized regression coefficients are presented for the relationship between salivary cortisol and physical performance with salivary cortisol in quartiles (the lowest quartile being the reference quartile). <sup>†</sup> Adjusted for age, alcohol use, body mass index, physical activity and region.

## Relationship between cortisol and physical performance

Use of oral estrogens is known to affect CBG. However, excluding these participants (n=11 in the second cycle; n=16 in the fourth cycle) did not affect the results. To increase the power, we did not exclude these participants from the analyses.

## Discussion

The results of this study show that in older women there is a relationship between serum free cortisol and physical performance. This relationship can for the greater part be explained by the relationship between serum free cortisol and the performance on the tandem stand test. These findings in older women were confirmed by the relationships between evening salivary cortisol and physical performance and in particular the tandem stand. The results also show that in older men there is a relationship between evening salivary cortisol and physical performance. This relationship can for the greater part be explained by the chair stands and walk test.

In our study, relationships between cortisol and physical performance were found both in women and men, although differently for the individual performance tests. In women, cortisol was negatively associated with the tandem stand, which mainly measures balance. In one study, a relationship was observed between leg muscle power (force x velocity, the ability to generate force

**Table 5.** Relationship between evening salivary cortisol and the individual performance tests

		Tandem stand		Walk test		Chair stands	
		OR	p-value	OR	p-value	OR	p-value
<b>Women</b>							
evening salivary cortisol	Q1	1		1		1	
	Q2	1.71	0.08	0.83	0.44	1.29	0.28
	Q3	1.12	0.72	0.69	0.12	0.99	0.97
	Q4	2.79	<0.001	1.41	0.17	1.77	0.02
evening salivary cortisol (adjusted) <sup>†</sup>	Q1	1		1		1	
	Q2	1.92	0.05	0.77	0.30	1.34	0.23
	Q3	1.02	0.96	0.62	0.06	0.88	0.61
	Q4	2.42	0.008	1.09	0.75	1.43	0.16
<b>Men</b>							
evening salivary cortisol	Q1	1		1		1	
	Q2	1.86	0.10	1.98	0.006	1.92	0.09
	Q3	1.50	0.29	1.44	0.15	1.59	0.07
	Q4	2.00	0.07	2.33	0.001	2.15	0.003
evening salivary cortisol (adjusted) <sup>†</sup>	Q1	1		1		1	
	Q2	1.34	0.48	1.61	0.07	1.62	0.06
	Q3	1.15	0.75	1.29	0.33	1.54	0.09
	Q4	1.20	0.66	1.88	0.02	1.81	0.03

Odds ratios (OR) for a poorer test result. Lowest quartile is the reference quartile.

<sup>†</sup> Adjusted for age, alcohol use, body mass index, physical activity, and region.

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quickly) and tandem gait (forward and backward walking, heel to toe, over a 20-foot distance), while no relationship was found between leg muscle strength and tandem gait.<sup>28</sup> This suggests that leg muscle power explains more of the variance in balance than leg muscle strength. Other investigators found that older women had lower strength and strength development rates than older men.<sup>29</sup> Possibly, decline in muscle power and consequently balance is more pronounced in older women than in older men. Alternatively, older women have less muscular reserve and earlier pass a threshold than older men, resulting earlier in perturbation of balance. Moreover, in older women, cortisol may influence muscle power rather than muscle strength alone.

In men, we found an independent relationship between evening salivary cortisol and performance on the chair stands and walk test. The chair stands test predominantly measures the functional strength of the proximal lower extremity muscles. One of the symptoms of Cushing's syndrome is weakness of the proximal muscles, mainly of the lower extremities.<sup>30</sup> Izquierdo et al (2001) found that the cortisol level accounted for 18 % and 40 % of the variance in maximal isometric knee extension strength in middle-aged and older men, respectively.<sup>5</sup> The current findings support the hypothesis that high cortisol levels affect proximal muscle strength and not general muscle strength. Contrastingly, no relationships between serum cortisol and the chair stands were found. The walk test measures a combination of strength, balance and coordination. In men, a relationship between cortisol and the chair stands (strength) was found, but not between cortisol and the tandem stand (balance). This may imply that the relationship between cortisol level and the walk test in men is explained by strength more than by balance. This study did not separately test coordination.

Serum free cortisol (i.e. cortisol/CBG) is a rather rough estimate of the actual free cortisol concentration. Especially at higher cortisol/CBG ratio's, cortisol levels exceed CBG binding capacity, and then free cortisol rises steeply. Free cortisol can also be calculated using an algorithm based on the law of mass action, with both CBG and albumin as the binding proteins and the dissociation constants as described by Lentjes et al. (1999).<sup>31</sup> Although the relationship between the cortisol/CBG ratio and algorithm-based free cortisol was non-linear (as expected), the coefficient of correlation was high ( $r > 0.95$ ,  $p < 0.001$ ). Repeating our analyses using the algorithm-based free cortisol instead of cortisol/CBG ratio did not essentially alter the results.

The fetal origins hypothesis proposes that disease in adult life may originate from permanent changes in the structure, physiology and metabolism of the fetal body as adaptation to undernutrition.<sup>32</sup> Adaptation of the HPA axis may be one such mechanism and associations have been found between low birth weight and elevated morning cortisol concentrations in healthy older men.<sup>33</sup> The relationships found in the current study between cortisol and physical performance may originate in the perinatal period when the HPA axis is programmed.



### Relationship between cortisol and physical performance

A strength of this study is that a second population (2001/2002) that only partly overlaps with the first (1995/1996) was used to validate our findings. Some participants of the second cycle died or withdrew from the study and participants younger than 65 in 1996 participated in the fourth cycle in 2002. About 43 % of the participants in the second cycle also took part in the fourth cycle and 54 % of the fourth cycle had participated in the second cycle. In addition, the sample is representative for the older population in the Netherlands.

Two limitations need to be mentioned. First, the significant results that were observed could be a consequence of multiple testing. However, when a stricter  $\alpha$  of 0.01 is used, in women, the relationships between serum free cortisol and physical performance and between any of the cortisol measures and the tandem stand remain significant. Also, in men, the relationship between salivary cortisol and physical performance remains significant. The relationship between salivary cortisol and the walk test and chair stands could be interpreted as a trend. Second, cortisol was measured only once per cycle, while serum cortisol levels are known to fluctuate strongly during the day and with stress.<sup>13,34,35</sup> A more reliable measure for serum cortisol may be obtained by 24-hour measurements or repeated measurement. However, the mean serum cortisol concentrations measured are realistic for the population and time measured.<sup>36</sup> In addition, a relationship was found despite of the time point of sampling and it remained significant after adjustment for confounding. Furthermore, the analyses were conducted with three different measures for cortisol and in two partly different populations. In the second cycle cortisol was measured in serum and in the fourth cycle cortisol was measured in evening saliva. Results for serum total and serum free cortisol were comparable, though the relationships between serum free cortisol and physical performance were somewhat stronger. Serum free cortisol is believed to be the biologically active part of the serum total cortisol,<sup>37</sup> and probably is a better measure than serum total cortisol to express the relationship with functional outcomes. Salivary cortisol concentrations are believed to be equivalent to serum free cortisol levels in this respect. Overall, the results found with serum free cortisol are supported by the results found with evening salivary cortisol. The small differences between the cycles can be explained by the time point of sampling (morning vs. evening) and by the participants measured. Cortisol levels fluctuate highly during the day, with a peak early in the morning and a nadir late in the evening.<sup>13,34,35</sup> The normal range for cortisol levels in the morning is wide. Serum cortisol shows a fluctuating pattern and morning serum cortisol better reflects peak cortisol, while evening salivary cortisol better reflects basal cortisol secretion.

We found a relationship between cortisol and physical performance in healthy older persons with cortisol levels fluctuating within the normal range. This relationship was for the greater part explained by the chair stands and walk test in men and by the tandem stand in women. As shown in Figure 2, over the full range of cortisol values measured, a difference of 2 points in



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physical performance was observed. A two points lower score indicates that the performance was one point lower on two of the three tests (25 % reduction in the score on two test) or two points lower on one of the three tests (a 50 % reduction in the score on one test) as compared with the higher score. To our knowledge, the clinical or population relevance of a one-point difference in physical performance in older persons has not yet been discussed in the literature. However, a high cortisol level appears to be a risk factor for a poorer physical performance score, and decline in physical performance is known to predict disability, recurrent falling and other health-related factors in older persons.<sup>21,22,38</sup> In an earlier study conducted at our department, recurrent fallers (mean score=6.1) scored 1.1 points lower on physical performance than non- and once-fallers (mean=7.2)<sup>38</sup>, indicating that a one-point difference can have a profound effect on one's health status. Furthermore, it is interesting to see that these relationships were found in a normal older population. It can be expected that the relationships will be even stronger in a less healthy population.

A possible mechanism explaining the effect of cortisol on physical performance is that glucocorticoids stimulate degradation and decrease synthesis of myosin heavy chains which leads to muscle atrophy.<sup>39</sup> Further research on the relationship between cortisol and muscle strength and the underlying mechanisms, both in men and women, is needed and may explain the different relationships found in women and men in this study. Furthermore, since performance on the tandem stand is associated with recurrent falling,<sup>40</sup> it might be interesting to examine the association between cortisol and recurrent falling.

In conclusion, high levels of cortisol are negatively associated with physical performance in healthy older persons. This association can for the greater part be explained by balance in women and by proximal leg strength in men.

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# 3

## **The relationship between cortisol, muscle mass and muscle strength in older persons and the role of genetic variations in the glucocorticoid receptor**

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Deelneemster onderzoek: “Ik ben een gevallen vrouw.”

**Abstract**

**Objective** Cortisol levels increase with age and hypercortisolism is associated with muscle weakness. This study examines the relationship between cortisol, muscle mass and muscle strength in community-dwelling older persons and the role of genetic variations in the glucocorticoid receptor (GR).

**Methods** The study was conducted within the Longitudinal Aging Study Amsterdam (LASA, 1992-ongoing), a cohort study in a population-based sample of older persons in the Netherlands. Data were used from 1196 and 1046 participants in the second (1995/1996) and fourth (2001/2002) cycle, respectively. Total serum cortisol and free cortisol were measured in the mornings of the second cycle while salivary cortisol sampled early in the morning and late at night were measured in the fourth cycle. The GR gene polymorphisms (ER22/23EK, N363S, 9beta and *BclI*) were genotyped by Taqman. Appendicular skeletal muscle mass (ASMM) was measured using DXA in the second cycle and three years later (third cycle). Grip strength was assessed using a handgrip dynamometer in the second, third, fourth and fifth cycle.

**Results** A relationship was found between both morning and evening salivary cortisol and loss of grip strength: participants in the highest quartile of cortisol concentration had a two fold higher risk of loss of grip strength than participants in the lowest quartile ( $p < 0.05$ ). No relationships were found between serum cortisol, (loss of) ASMM, and (loss of) grip strength. The ER22/23EK and N363S-polymorphisms modified the relationships between serum cortisol, ASMM and grip strength, respectively. Due to limited power, these relationships were not significant after stratification for the polymorphisms.

**Conclusion** High salivary cortisol is associated with a higher risk of loss of grip strength in older persons. GR genotypes seem to modify the relationship between muscle mass and muscle strength.

## Introduction

Sarcopenia, i.e. the age-related loss of muscle mass and muscle strength<sup>1</sup>, may lead to decreased physical activity and falls. Alteration in genetic and hormonal mechanisms as well as inactivity may predict these muscular changes.<sup>2-4</sup> Cortisol is known to stimulate degradation and inhibit synthesis of muscle proteins.<sup>3,5,6</sup> Conditions such as Cushing's syndrome or in glucocorticoid therapy where there is an excess of cortisol, are associated with muscle atrophy and weakness.<sup>5-8</sup> One study in 26 middle aged and 21 healthy older men found that cortisol levels were negatively related to muscle strength of the knee extensor.<sup>9</sup> In our previous study, a relationship between higher cortisol and poorer physical performance was observed.<sup>10</sup> It is not yet known whether similar relationships exist between cortisol and muscle strength in the general older population.

The circadian rhythm of the cortisol level is characterised by a peak in the morning (7am) and a trough level in the evening (11pm), which represent peak secretion and the basal level, respectively. In addition, cortisol levels fluctuate during the day and with stress.<sup>11-13</sup> Serum levels of cortisol are more sensitive to these fluctuations than salivary cortisol levels. Different associations with muscle parameters may be found for different time points and techniques of cortisol measurement.

The effects of glucocorticoids on target tissues are mediated by the glucocorticoid receptor (GR).<sup>14</sup> Four single nucleotide polymorphisms (SNPs) in the GR gene have been described: ER22/23EK,<sup>15,16</sup> N363S,<sup>16</sup> 9beta,<sup>17</sup> and BclI.<sup>18</sup> These polymorphisms appear to be associated with altered sensitivity to glucocorticoids, changes in body composition, low bone mineral density, and more severe coronary artery disease,<sup>18-21</sup> and may be associated with changes in muscle mass and strength.

We aimed to assess the relationship between cortisol levels and muscle mass and muscle strength in older men and women. We hypothesised that high cortisol levels were associated with lower muscle mass and muscle strength and higher rates of loss over time. In addition, the role of GR gene polymorphisms in these relationships was studied as well.

## Method

### *Subjects*

The study was performed within the Longitudinal Aging Study Amsterdam (LASA), an ongoing interdisciplinary cohort study on predictors and consequences of changes in physical, cognitive, emotional and social functioning in older persons.<sup>22</sup> A random sample of older men and women stratified for age, sex and expected five years mortality was drawn from the population registry of eleven municipalities within the west, northeast and south of the Netherlands. The sample represents the older Dutch population with respect to geographic region and degree

of urbanization. The sampling and data collection procedures have been described in detail elsewhere.<sup>23</sup> The sample for this study included participants who took part in the main and medical interview of the second and fourth cycle of LASA (1995/1996 and 2001/2002). The exact numbers of participants per cycle are described in the next paragraphs. In the second cycle, cortisol was measured in the morning using blood samples. The glucocorticoid receptor (GR) polymorphisms were determined using these same blood samples. Grip strength was measured in the total sample and appendicular skeletal muscle mass (ASMM) was measured in a sub-sample (i.e. participants living in Amsterdam and vicinity). In the fourth cycle, cortisol was measured in the morning and in the evening using saliva samples. Grip strength was measured in the total sample. In this cycle, ASMM and GR polymorphisms were not measured. All other variables were assessed in a similar way in the main and medical interviews in both the second and fourth cycle. Both the second and fourth cycles were included, because different methods were used to measure cortisol and, as explained in the introduction, this may lead to different results. The Ethical Review Board of the VU University Medical Center approved the study and all participants signed informed consent.

**Second cycle:** Participants in the second cycle were born before 1930 (aged 65 and older as of January 1, 1996). In total, 1509 participants were asked to provide blood samples, and blood samples were obtained in 1331 participants. No blood samples could be obtained in 178 participants, 1 had an incorrect value and in 51 samples no cortisol level could be determined. Of the 1279 participants with valid serum cortisol values, those using oral corticosteroids or sex hormones ( $n=28$ ) or having a knee prosthesis ( $n=11$ ) were excluded. After excluding participants with missing values on the confounders ( $n=44$ ), complete data were available of 1196 (grip strength) and 482 (ASMM) participants. Participants without cortisol levels, were older ( $p=0.008$ ), more often women ( $p=0.006$ ) and smokers ( $p=0.04$ ), and drank less alcohol ( $p<0.001$ ).

**Fourth cycle:** Participants in the fourth cycle were born before 1936 (aged 65 and older as of January 1, 2002). In total, 1691 participants were asked to collect saliva samples and 1223 participants provided at least one sample. Reasons for nonresponse were: deceased ( $n=8$ ), refusals ( $n=187$ ), ineligible ( $n=21$ ), technical error ( $n=1$ ) and could not be contacted ( $n=251$ ). Of these 1223 participants, 15 evening samples had insufficient volume, 103 were below the detection limit and 5 had levels higher than 100 nmol/l, which were likely to be due to measurement error, and were excluded. Of the remaining 1100 participants, 1082 had valid grip strength measurements. Of the 1223 participants, 18 morning samples had insufficient volume, 18 fell below the detection limit and 10 had levels higher than 100 nmol/l, and were excluded from the analyses. Of the remaining 1177 participants, all had valid grip strength measurements. Participants using oral corticosteroids or sex hormones ( $n=88$  and  $n=86$ ) and participants with



missing values on the confounders ( $n=43$  and  $n=38$ ) were excluded. Complete data sets were available for 1046 and 958 participants, respectively. Participants using oral corticosteroids or sex hormones ( $n=88$  and  $n=86$ ) and participants with missing values on the confounders ( $n=43$  and  $n=38$ ) were excluded. Complete data sets were available for 1046 and 958 participants, respectively. Participants without salivary cortisol levels, were older ( $p<0.001$ ), were more often women (67.8 %,  $p<0.001$ ), had more depressive symptoms ( $p<0.001$ ) and drank less alcohol ( $p=0.03$ ). Of all participants included, 513 participated in both cycles.

### *Measurements*

#### *Serum cortisol, corticosteroid binding globulin and albumin*

Participants were invited to a health care center near their homes where blood samples were collected in the morning; participants were allowed to take only tea and toast before drawing blood. Most participants had their blood samples taken before 10am. The blood samples were centrifuged and serum was stored at  $-70^{\circ}\text{C}$  until processing in 2002/2003. The serum levels of cortisol were determined using a competitive immunoassay (ACS: Centaur, Bayer Diagnostics, the Netherlands). The concentrations of serum cortisol did not fall below the lower detection limit of 30 nmol/l, and the inter-assay coefficients of variation (CV) were 6 % at 150 nmol/l and 8 % at 1000 nmol/l.

Corticosteroid binding globulin (CBG) levels were determined using a radio-immunoassay method (Medgenix Diagnostics, Belgium). The concentrations of CBG did not fall below the lower detection limit of 11 mg/l in any of the samples, the inter-assay CV's were 8 % at 30 mg/l and 5 % at 110 mg/l. Albumin levels were determined using a Bromcresol Green Photometric Assay with a Hitachi analyser (Zwolle) or a Bromcresol Purple method (Amsterdam and Oss).<sup>24</sup> To make the albumin levels comparable, levels that were determined using the Bromcresol Purple method were converted using a validated formula.<sup>25</sup> Algorithm-based free cortisol was calculated using an algorithm based on the law of mass action, with both CBG and albumin as the binding proteins and the dissociation constants as described by Lentjes et al (1999).<sup>26</sup>

#### *Salivary cortisol*

In the fourth cycle, saliva samples were collected using cotton balls (Salivettes). The procedure has been described in more detail elsewhere.<sup>10</sup> Briefly, the cotton balls were chewed for 90 seconds, 30 minutes after awakening (morning sample) and at approximately 2300h (night sample). The samples were kept refrigerated at  $-20^{\circ}$  until processing. Radioimmunoassay coated tubes (Spectria Orion Diagnostics, Finland) were used to determine morning and evening salivary cortisol (in duplicate). None of the measured salivary cortisol concentrations fell below the lower detection limit of 1.5 nmol/l. The intra- and inter-assay coefficients of variation (CV) were less than 19 %. Salivary cortisol, as measured by Salivettes, reliably represent serum cortisol.<sup>27,28</sup>

*Single Nucleotide Polymorphisms (SNP)*

Genomic DNA was extracted from the same blood samples as the serum cortisol according to standard procedures. Genotypes were determined using the Taqman allelic discrimination assay. The Assay-by-Design service (<http://www.appliedbio-systems.com>) was used to set up a Taqman allelic discrimination assay for ER22/23EK, N363S, 9beta, and *BclI*. The exact procedure was described in detail elsewhere.<sup>20</sup> Primer and probe sequences are available on request. Results were analyzed by the ABI Taqman 7900HT using the sequence detection system 2.22 software (Applied Biosystems Inc.). To confirm the accuracy of genotyping results, 80 randomly selected samples were re-genotyped using the same method and yielded similar results.

*(Loss of) Appendicular skeletal muscle mass (ASMM)*

Body composition was measured in a subsample of the second cycle using dual-energy x-ray absorptiometry (DXA, Hologic QDR 2000 scanner, software version V5.70A, Hologic Inc., Waltham, MA). ASMM was calculated as the sum of fat-free and bone-free mass of the arms and legs (grams). This method has been validated in older persons.<sup>29</sup> Three years after the second cycle, this procedure was repeated (third cycle). Change in ASMM was calculated as  $((ASMM_{95/96} - ASMM_{98/99}) / ASMM_{95/96}) \cdot 100\%$ . Loss of ASMM was defined as 3 % loss of ASMM or more, approximating the highest 15 % of the sample. A change of 3 % or more is likely not to represent measurement error.<sup>30</sup>

*(Loss of) Grip strength*

Grip strength was measured using a calibrated strain-gauged dynamometer (Takei TKK 5001, Takei Scientific Instruments Co. Ltd., Tokyo, Japan). All participants were asked to perform two maximum grip strength trials with each hand, while standing with their arm along the body. Grip strength was calculated in each case as the mean of the maximum scores of the left and right hand (kilograms). Three years after the second (third cycle) and four years after the fourth cycle (fifth cycle), this procedure was repeated and change in grip strength was calculated as  $((\text{grip strength}_{95/96} - \text{grip strength}_{98/99}) / \text{grip strength}_{95/96}) \cdot 100\%$  in the second cycle and  $((\text{grip strength}_{01/02} - \text{grip strength}_{05/06}) / \text{grip strength}_{01/02}) \cdot 100\%$  in the fourth cycle. Loss of grip strength was defined the 15 % of the sample with the highest loss of grip strength (in accordance with the definition for loss of ASMM). The cut-off values for the highest 15 % were 38 % and 21 % loss of grip strength in the second and fourth cycles, respectively.

*Effect modifier*

In our previous study, sex differences were found in the relationship between cortisol and physical performance.<sup>10</sup> Moreover, sex differences were found in the basal activity of the hypothalamic-pituitary-adrenal (HPA) axis<sup>12</sup> and the response of the HPA-axis to challenge.<sup>31</sup> Thus, the relationships between cortisol, muscle mass and strength may differ for men and women.

*Potential confounders*

Age was derived from the municipal registries. Region was assessed as living in the west (Amsterdam and vicinity), east (Zwolle and vicinity) or south (Oss and vicinity) of the Netherlands. Body weight and height were used to calculate the body mass index ( $\text{BMI} = \text{mass (kg)}/\text{height (m)}^2$ ). Total body fat was measured using DXA. Alcohol consumption (drinking alcohol, 0 vs. 1-14 vs. 15 glasses or more per week) and smoking (current smoker, yes/no) were assessed during an interview. The presence of chronic diseases was assessed with a questionnaire on self-reported chronic diseases, which included chronic non-specific lung diseases, cardiac and vascular diseases, stroke, diabetes mellitus, malignant neoplasms, and joint disorders (i.e. osteoarthritis and rheumatoid arthritis). Chronic non-specific lung disease (CNSLD) was used as a separate variable, since the association between cortisol and chronic non-specific lung diseases may be reversed compared to the other diseases (personal communication with RMM Schoorlemmer, 2007). The other diseases were summed as the number of chronic diseases (range 0-6). Depressive symptoms were assessed using the Center for Epidemiologic Studies-Depression scale (CES-D, range 0-60).<sup>32</sup> Medication use was assessed by recording the medications of the participant directly from the containers. Mini-Mental State Examination (MMSE) was used to estimate cognitive functioning (range 0-30).<sup>33</sup> Creatinine, oestradiol, and 25-hydroxyvitamin D (25-OHD) were determined in the same blood samples as the serum cortisol levels (second cycle) using standard laboratory procedures. These biomarkers as well as total body fat were not measured in the fourth cycle.

*Statistical analysis*

Data were analyzed using SPSS 14.0.1 (SPSS Inc, Chicago III). Baseline characteristics were presented as means and standard deviations (SD) for normally distributed variables, medians and interquartile ranges (IQR) for skewed variables and percentages for dichotomous variables. The following steps were conducted for each of the outcome measures. First, linearity was checked for the relationships between cortisol and the outcome measures. Second, it was tested whether the interaction with sex was significant ( $p < 0.10$ ). Third, univariate regression analysis was conducted. Linear regression was used for the continuous outcomes (ASMM and grip strength) and logistic regression was used for the dichotomous outcomes (loss of ASMM and loss of grip strength). Fourth, multivariate regression analysis was performed with adjustment for those confounders that led to a change of more than 10 % in the regression coefficient of the relationships between cortisol and the outcome measures. The relationships were considered statistically significant at  $p < 0.05$ .

For the genetic analyses, Hardy-Weinberg Equilibrium (HWE) was calculated according to standard procedures using Chi-square analysis. The mean cortisol, mean ASMM and mean grip strength were described per genotype. ANCOVA was used to test for significant differences in

cortisol, ASMM and grip strength. In addition, the genotypes were tested for interaction in the relationships between cortisol, ASMM and grip strength ( $p < 0.10$ ).

## Results

Baseline characteristics for the second and fourth cycle are shown in Table 1. Cortisol was not linearly related to any of the outcome measures. Therefore, all analyses were performed with cortisol in quartiles. The interaction with sex was not significant ( $p > 0.17$ ). Therefore, all analyses were done for men and women combined. Table 2 presents the cortisol ranges per quartile.

**Table 1.** Baseline data in the second and fourth cycle

	Second cycle (1995/1996)		Fourth cycle (2001/2002)	
	n		n	
Sex (% women)	1196	50.3	1046	51.8
Age (years)	1196	75.4 (6.5)	1046	74.5 (7.0)
Region (% Amsterdam)	1196	46.7	1064	42.3
Height (cm)	1196	166.5 (9.0)	1064	167.9 (9.4)
Body mass index (kg/m <sup>2</sup> )	1196	26.9 (4.2)	1046	27.4 (4.2)
Total body fat (kg) <sup>#</sup>	482	26.7 (9.9)		-
Smoking (% yes)	1196	18.6	1046	14.9
Number of chronic diseases <sup>‡</sup>	1196	1 [0-3]	1046	1 [0-3]
CNSLD (% yes)	1196	14.9	1046	12.8
CES-D (0-60) <sup>‡</sup>	1168	6 [0-15]	957	7 [0-16]
MMSE (0-30) <sup>‡</sup>	1196	28 [25-30]	1046	28 [26-30]
Creatinine (nmol/l) <sup>‡</sup>	1196	90 [66-114]		-
Albumin (nmol/l)	1196	41.9 (3.9)		-
Estradiol (nmol/l) <sup>‡</sup>	1189	49.4 [1.5-97.2]		-
25-OHD (nmol/l)	1196	53.8 (24.3)		-
ASMM (g) <sup>#</sup>	482	18054 (4248)		-
Change in ASMM <sup>##</sup>	310	-1.6 [-8.1- 4.9]		-
Grip strength (kg)	1196	28.3 (9.8)	1046	28.0 (10.5)
Change in grip strength <sup>‡</sup>	1131	8.7 [-1.3- 22.4]	760	4.8 [-17.5- 27.1]
Serum total cortisol (nmol/l)	1196	498.4 (168.7)		-
Algorithm based-free cortisol <sup>‡</sup>	1131	29.2 [0.8-57.6]		-
Morning salivary cortisol (nmol/l) <sup>‡</sup>		-	1046	15 [6.0-24.0]
Evening salivary cortisol (nmol/l)		-	958	3 [1.1-4.9]

All results are presented in mean (standard deviation) unless stated otherwise; <sup>‡</sup> Results are presented in median [interquartile range]; <sup>#</sup> Measured in a sub sample of 482 participants; CNSLD Chronic Non-Specific Lung Disease; CES-D Center for Epidemiological Studies-Depression scale; MMSE Mini Mental State Examination; 25-OHD 25-hydroxyvitamin D; ASMM Appendicular Skeletal Muscle Mass

**Table 2.** Ranges of the cortisol quartiles per model

	<b>Second cycle</b>		<b>Fourth cycle</b>	
	<b>(loss of) ASMM</b>	<b>(loss of) grip strength</b>	<b>(loss of) ASMM</b>	<b>(loss of) grip strength</b>
	Serum total cortisol <sup>#</sup>		Morning salivary cortisol <sup>#</sup>	
Q1	89-330	30-380	-	1.6-10.7
Q2	331-419	381-473	-	11.0-14.0
Q3	420-533	474-604	-	15.0-19.0
Q4	534-997	605-1236	-	20.0-73.0
	Algorithm-based free cortisol		Evening salivary cortisol <sup>#</sup>	
Q1	3.0-14.8	0.8-18.1	-	1.5-2.3
Q2	14.8-23.1	18.1-29.2	-	2.4-3.0
Q3	23.1-36.4	29.2-46.5	-	3.1-4.3
Q4	36.4-121.1	46.5-168.2	-	4.4-62.0

<sup>#</sup>Cortisol values are presented in nmol/l (=27.5µg/dl)

**Table 3.** The relationship between serum cortisol and ASMM

	<b>Mean ASMM</b>	<b>Regression coefficient</b>	<b>CI</b>	<b>p-value</b>
Serum total cortisol				
Q1	17,369	0		
Q2	18,052	682	-382 to 1746	0.21
Q3	19,020	1,651	804 to 3,565	0.003
Q4	17,814	444	-267 to 2,437	0.42
Adjusted				
Q1	18,241	0		
Q2	17,930	-311	-587 to -35	0.03
Q3	18,062	-178	-466 to 109	0.22
Q4	18,026	-215	-497 to 67	0.14
Algorithm-based free cortisol				
Q1	15,896	0		
Q2	17,937	2,041	983 to 3,099	<0.001
Q3	19,295	3,399	2,338 to 4,459	<0.001
Q4	18,999	3,103	2,038 to 4,4168	<0.001
Adjusted				
Q1	18,171	0		
Q2	18,119	-52	-345 to 241	0.73
Q3	17,936	-235	-548 to 78	0.14
Q4	17,960	-211	-526 to 106	0.19

Means (g), regression coefficients and 95 % Confidence Intervals (CI) presented for the relationship between serum cortisol and ASMM adjusted for sex, age, BMI, height, body fat, smoking, chronic diseases and CNSLD. Lowest cortisol quartile is the reference quartile

*Appendicular skeletal muscle mass*

In the second cycle, ASMM was measured in 482 participants. The mean ASMM was 18,054 grams (SD=4,248). After adjustment for the confounders, participants in the highest cortisol quartiles had lower ASMM than the participants in the lowest quartiles. However, except for the second versus the lowest serum total cortisol quartile ( $p=0.03$ ), these relationships were not significant (Table 3). Loss of ASMM was measured in 310 participants and 47 participants had a loss of 3 % or more. The median change of ASMM was -1.6 % (IQR=-8.1-5.0) (the negative sign indicates a gain in ASMM). No significant relationships were found between serum cortisol and loss of ASMM (data not shown).

*Grip strength*

In the second cycle, both serum cortisol and grip strength were measured in 1196 participants. The mean grip strength was 28.3 kg (SD=9.8). In the fourth cycle, both morning salivary cortisol and grip strength were measured in 1046 participants and both evening salivary cortisol and grip strength were measured in 958 participants. The mean grip strength was 28.0 kg (SD=10.5). After adjustment for confounding, no significant relationships were found between any of the cortisol measures and grip strength (Table 4).

In the second cycle, loss of grip strength was measured in 912 participants and 137 participants had a loss of 38 % or more. The median change of grip strength was 8.7 % (IQR=-1.3-22.4). After adjustment for the confounders, the relationships between serum total and free cortisol and loss of grip strength were not significant (Table 4). In the fourth cycle, loss of grip strength was measured in 760 participants and 114 participants had a loss of 21 % or more. The median change of grip strength was 4.9 % (IQR=-18.0-27.8). After adjustment for the confounders, participants in the second, third and fourth (highest) morning salivary cortisol quartiles had a 2 times higher risk of loss of grip strength than the participants in the lowest quartile ( $p<0.05$ ). In addition, the participants in the fourth (highest) evening cortisol quartile had a 2.4 times higher risk of loss of grip strength than the participants in the lowest quartile ( $p=0.005$ ).

*Role of genetic variations in the glucocorticoid receptor*

Table 5 shows the frequencies per genotype. All SNPs were in HWE, except for the ER22/23EK SNP. Only 0.4 % of the participants were homozygous (AA) for the ER22/23EK SNP. For analytical purposes, these carriers were combined with the heterozygotes (GA). After adjustment, no significant differences in mean serum total cortisol, free cortisol, ASMM and grip strength were found between the genotypes (Table 6). None of the participants were homozygous (GG) for the N363S SNP. After adjustment, no significant differences in mean serum total cortisol, free cortisol, ASMM and grip strength were found between the genotypes. The GG genotype for the 9beta SNP was found in only 3.7 % of the participants. These participants were combined

**Table 4.** Relationship between cortisol and (loss) of grip strength

	Grip strength <sup>#</sup>			Loss of grip strength <sup>‡</sup>			
	b	CI	p-value	b	CI	p-value	
Second cycle	Serum total cortisol (n=1196)			(n=912)			
	Q1	0		I			
	Q2	0.81	-0.76 to 2.38	0.31	0.80	0.50 to 1.29	0.37
	Q3	2.14	0.58 to 3.70	0.007	0.75	0.46 to 1.21	0.24
	Q4	1.89	0.32 to 3.46	0.02	0.42	0.24 to 0.74	0.002
	Adjusted						
	Q1	0		I			
	Q2	-0.27	-1.14 to 0.60	0.54	1.08	0.64 to 1.84	0.77
	Q3	0.31	-0.58 to 1.20	0.50	1.31	0.76 to 2.28	0.34
	Q4	-0.03	-0.93 to 0.88	0.95	0.76	0.40 to 1.43	0.40
	Algorithm-based free cortisol (n=1131)			(n=888)			
	Q1	0		I			
	Q2	3.01	1.43 to 4.60	<0.001	0.66	0.40 to 1.09	0.11
	Q3	4.20	2.62 to 5.79	<0.001	0.81	0.50 to 1.30	0.37
	Q4	5.07	3.48 to 6.66	<0.001	0.43	0.24 to 0.75	0.003
	Adjusted						
Q1	0		I				
Q2	0.41	-0.48 to 1.29	0.37	0.76	0.43 to 1.33	0.34	
Q3	0.04	-0.87 to 0.95	0.93	1.30	0.73 to 2.31	0.38	
Q4	0.18	-0.77 to 1.12	0.72	0.66	0.33 to 1.30	0.23	
Fourth cycle	Morning salivary cortisol (n=1046)			(n=760)			
	Q1	0		I			
	Q2	1.16	-0.66 to 2.98	0.21	2.27	1.20 to 4.27	0.01
	Q3	0.33	-1.42 to 2.08	0.71	1.95	1.04 to 3.65	0.04
	Q4	-0.15	-0.26 to 2.12	0.87	2.04	1.07 to 3.89	0.03
	Adjusted						
	Q1	0		I			
	Q2	-0.78	-0.40 to 1.97	0.20	2.20	1.13 to 4.26	0.02
	Q3	-0.48	-0.66 to 1.62	0.41	2.09	1.09 to 4.02	0.03
	Q4	-0.93	-0.26 to 2.12	0.13	1.97	1.00 to 3.87	0.05
	Evening salivary cortisol (n=958)			(n=692)			
	Q1	0		I			
	Q2	-0.74	-2.60 to 1.12	0.43	1.11	0.59 to 2.08	0.75
	Q3	-0.63	-2.47 to 1.21	0.50	1.32	0.72 to 2.42	0.37
	Q4	-1.79	-3.68 to 0.09	0.06	2.62	1.48 to 4.66	0.001
	Adjusted						
Q1	0		I				
Q2	-0.55	-1.79 to 0.66	0.37	1.12	0.58 to 2.15	0.74	
Q3	-0.38	-1.58 to 0.83	0.54	1.28	0.68 to 2.41	0.44	
Q4	-1.05	-2.29 to 0.19	0.10	2.39	1.31 to 4.38	0.005	



Footnote Table 4. Regression coefficients (b), Odds ratios (OR) and 95 % Confidence Intervals (CI) are presented unadjusted and adjusted for <sup>#</sup> age, sex, region, BMI, height, MMSE, chronic diseases, CNLSD, and in the second cycle albumin and 25-OHD; <sup>‡</sup> age, sex, region, BMI, height, chronic diseases, and baseline grip strength, and additionally for albumin in the second cycle. The lowest quartile is the reference quartile.

with the heterozygotes (AG). After adjustment, the 9beta-carriers tended to have 25 nmol/l lower cortisol levels than the non-carriers (AA=500 nmol/l, AG+GG=475 nmol/l,  $p=0.05$ ). The genotypes did not differ with respect to mean free cortisol, ASMM and grip strength. The *BclI*-carriers and non-carriers did not differ in mean serum total cortisol, free cortisol, ASMM and grip strength.

An interaction with the ER22/23EK polymorphism was found in the relationship between serum total cortisol and ASMM ( $p=0.04$ ). After stratification, no significant relationships were found in the ER22/23EK-carriers and non-carriers (Table 7). Also, an interaction with the N363S polymorphism was found in the relationship between serum total cortisol and grip strength ( $p=0.09$ ). In the non-carriers, no significant relationship was found between serum total cortisol and grip strength. The N363S-carriers in the second and third quartiles tended to have 3.8 and 4.7 kg higher grip strength than the carriers in the lowest quartile ( $p=0.06$  and

**Table 5.** Hardy-Weinberg Equilibrium (HWE) and frequencies per genotype

Polymorphism	Genotype	HWE p-value	n (%) <sup>#</sup>	combined n (%)
<b>ER22/23EK</b>		0.04		
	GG <sup>w</sup>		760 (93.3)	760 (93.3)
	GA <sup>he</sup>		52 (6.4)	55 (6.7)
	AA <sup>ho</sup>		3 (0.4)	
<b>N363S</b>		0.33		
	AA <sup>w</sup>		761 (93.4)	
	AG <sup>he</sup>		54 (6.6)	
	GG <sup>ho</sup>		0	
<b>9beta</b>		0.17		
	AA <sup>w</sup>		563 (69.1)	563 (69.1)
	AG <sup>he</sup>		222 (27.2)	252 (30.9)
	GG <sup>ho</sup>		30 (3.7)	
<b>BclI</b>		0.93		
	CC <sup>w</sup>		348 (42.7)	
	CG <sup>he</sup>		370 (45.4)	
	GG <sup>ho</sup>		97 (11.9)	

Hardy-Weinberg Equilibrium (HWE) and frequencies are presented for the wild type (w), heterozygote (he) and homozygote (ho) genotypes; <sup>#</sup> ASMM was measured in a sub sample (n=455) but the percentages of the genotypes were similar to the percentages in the total sample.



**Table 6.** Mean serum cortisol, ASMM and grip strength: differences in genotypes

<b>Genotype</b>	<b>serum total cortisol (nmol/l)<sup>#</sup></b>	<b>algorithm-based free cortisol<sup>#</sup></b>	<b>ASMM (g)<sup>‡</sup></b>	<b>grip strength (kg)<sup>†</sup></b>
<b>ER22/23EK</b>				
p-value	0.65	0.72	0.85	0.84
GG	492	34.8	17,994	28.3
GA+AA	492	37.7	19,017	30.6
<b>N363S</b>				
p-value	0.31	0.55	0.23	0.35
AA	494	35.2	17,946	28.3
AG	464	33.1	19,438	29.8
GG	-	-	-	-
<b>9beta</b>				
p-value	0.05	0.15	0.36	0.41
AA	499	35.7	18,067	28.3
AG+GG	476	33.6	18,037	28.8
<b>BcII</b>				
p-value	0.52	0.49	0.63	0.57
CC	493	33.9	17,882	27.9
CG	487	35.6	18,395	29.0
GG	510	37.0	17,281	28.0

Unadjusted means are presented for the genotypes. Differences are tested using ANCOVA and p-values are presented after adjustment for <sup>#</sup> age, sex, BMI, region, depression, chronic diseases, and CNSLD; <sup>‡</sup> age, sex, BMI, height, body fat, smoking, chronic diseases, and CNSLD; <sup>†</sup> age, sex, region, height, BMI, chronic diseases, CNSLD, MMSE, 25-OHD, and albumin.

p=0.07, respectively). No interactions were found with the 9beta and BcII polymorphisms in the relationships between cortisol, ASMM and grip strength (data not shown).

## Discussion

To our knowledge, this is the first study that investigated the relationship between natural levels of cortisol, muscle mass, and muscle strength in a population-based sample of older persons. Older persons with high salivary cortisol levels had an increased risk of loss of grip strength. However, no relationships were found between serum cortisol and (loss of) grip strength and ASMM. In addition, this is the first study that investigated the role of the GR polymorphisms with regard to muscle mass and muscle strength in older persons. We found that the ER22/23EK and N363S polymorphisms modified the relationships between serum cortisol and ASMM and grip strength, respectively.

**Table 7.** Relationships between serum total cortisol and ASMM stratified for ER22/23EK, and between serum total cortisol and grip strength stratified for N363S

	Non-carriers			Carriers		
	regression coefficient	CI	p	regression coefficient	CI	p
Relationship between serum total cortisol and ASMM stratified for ER22/23EK <sup>#</sup>						
Q1	0			0		
Q2	-275	-564 to 14	0.06	-511	-2107 to 1085	0.51
Q3	-142	-438 to 154	0.35	-501	-2696 to 1695	0.64
Q4	-190	-487 to 106	0.21	-503	-2218 to 1213	0.54
Relationship between serum total cortisol and grip strength stratified for N363S <sup>‡</sup>						
Q1	0			0		
Q2	-0.28	-1.32 to 0.76	0.60	3.84	-0.21 to 7.89	0.06
Q3	0.44	-0.61 to 1.50	0.41	4.72	-0.46 to 9.90	0.07
Q4	0.26	-0.84 to 1.35	0.65	0.16	-5.37 to 5.69	0.95

Presented are the regression coefficients, 95 % Confidence Intervals (CI) and p-values after adjustment for <sup>#</sup> age, sex, BMI, height, body fat, smoking, chronic diseases, and CNSLD; <sup>‡</sup> age, sex, region, BMI, height, MMSE, chronic diseases, and CNSLD. Lowest cortisol quartile is the reference quartile.

#### *Appendicular skeletal muscle mass*

With aging, type II muscle fibres (fast-twitch) have been found to decrease in area, number and size, resulting in a decrease in muscle mass.<sup>34-36</sup> Glucocorticoid-mediated muscle atrophy has been found to affect mainly type II muscle fibers.<sup>5,37,38</sup> Based on these findings, cortisol is expected to affect type II muscle fibres and consequently muscle mass. Only one study has investigated the relationship between cortisol and muscle mass before, and this study found a negative correlation between morning serum cortisol and the cross-sectional area of the quadriceps femoris muscle in 21 older men.<sup>9</sup> In the current study, participants with high cortisol levels had lower muscle mass, however not significantly. The difference in findings may be explained by differences in sample size, population and the statistical analyses used. First, the sample size in the current study is larger (482 versus 21) and the average age is higher (75 versus 65 years). If there were a relationship, it would sooner be found in a larger and older sample. Second, the relationship may be different in women and men. The current study includes both women and men; however, no interaction with sex was found. Third, this study reports adjusted regression models, while Izquierdo et al (2001) reported unadjusted correlation coefficients. In our study, confounders such as age, height, BMI, and body fat explained the associations. In conclusion, the current results do not support the hypothesis that variations in normal levels of cortisol are associated with variations in muscle mass in older persons.

*Grip strength*

Negative effects on muscle strength have been found after long-term exposure to high levels of cortisol.<sup>39,40</sup> In line with the literature, we found that high morning and evening salivary cortisol was associated with a two-fold higher risk of loss of grip strength between 2001/02 and 2005/06. However, no relationship was found between serum cortisol and loss of grip strength between 1995/96 and 1998/99. Serum cortisol levels are known to fluctuate during the day and with stress, salivary cortisol levels are less sensitive to these fluctuations and therefore believed to be a more reliable measure for free cortisol.<sup>11,13</sup> In the second cycle, albumin was found to be a confounder, this variable was not measured in the fourth cycle. A third explanation may be, that the interval between the baseline and follow up measurement in the second cycle is 3 years and 4 years in the fourth cycle. Longer follow-up interval may lead to a greater loss of grip strength and thus a larger chance to find a relationship. Future research is necessary to reveal whether there is a relationship between salivary cortisol and loss of grip strength independent of albumin.

Physical activity is a commonly used confounder in studies on ASMM and grip strength. Neither in the literature nor in the current sample, significant associations have been found between cortisol and level of physical activity. Therefore, physical activity did not fulfil the criteria of confounding and was not included as a confounder.

*Role of genetic variations in the glucocorticoid receptor*

The ER22/23EK polymorphism has been associated with decreased glucocorticoid sensitivity.<sup>41</sup> A study among young adults found that the male ER22/23EK-carriers had more muscle mass and strength, whereas in women only tendencies towards lower amounts of body fat were observed.<sup>19</sup> These findings could not be confirmed in the current study among older persons, even though the ER22/23EK polymorphism did modify the relationship between serum cortisol and muscle mass. No significant relationships were found after stratification for genotype, although, this may be due to the small number of participants per quartile.

The N363S polymorphism has been associated with increased sensitivity to cortisol.<sup>42</sup> In this study, the N363S polymorphism modified the relationship between cortisol and grip strength. No significant relationship was found in the non-carriers, while, in contrast to our expectations, the N363S-carriers in the middle serum cortisol quartiles tended to have a 4 kg higher grip strength than the carriers in the lowest quartile. However, the results must be interpreted with caution and may be caused by multiple testing or due to the small numbers of participants per quartile.

The strengths of this study are that two partly different samples were measured, that different cortisol measures (i.e. serum/salivary, morning/evening) were used and that muscle mass and

muscle strength were repeatedly measured in the same sample. Two limitations need to be mentioned. First, serum cortisol was measured only once in the second cycle. Cortisol is known to fluctuate strongly during the day and with stress.<sup>11-13</sup> These fluctuations are less pronounced in salivary cortisol. Therefore, a more reliable measure for basal levels (evening salivary cortisol) was also used in this study. Second, the significant relationships found may be caused by multiple testing, however, the results found are biologically plausible. Third, lack of significance may be due to limited power (type two error). To test this, we calculated the effect sizes of the relationships that were not significant. If the effect size is substantial ( $>0.30$  for medium effects and  $>0.80$  for large effects)<sup>43</sup> while the relationship is not significant, this may indicate a power problem. In this study, effect sizes of 0.30 and larger (data not shown) have been found for the relationship between total and free serum cortisol and loss of ASMM and between total and free serum cortisol and loss of grip strength. Further research in larger samples is necessary to confirm these relationships.

In conclusion, high salivary cortisol is associated with increased risk of loss of grip strength in older persons. The results of this study also suggest that some polymorphisms of the glucocorticoid receptor gene may modify the relationships between cortisol, muscle mass and muscle strength.

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# 4

## **Relationships between cortisol level, mortality and chronic diseases in older persons**

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oma: “Ik weet niet of er nog iets is na de dood, maar ik weet wel dat het hetzelfde is voor mij als voor iedereen.”

**Abstract**

**Objective** High cortisol level is known to be associated with osteoporosis, hypertension, diabetes mellitus, susceptibility to infections, and depression and may protect against chronic obstructive pulmonary disease (COPD). This study assesses the association between cortisol level, 6-7.5 year mortality risk and prevalence of chronic diseases.

**Methods** Subjects were selected from the Longitudinal Aging Study Amsterdam (LASA), an ongoing multidisciplinary cohort study in a general population of older persons ( $\geq 65$  years). Serum cortisol was measured in 1181 men and women in 1995/96 (second cycle) and salivary cortisol in 998 men and women in 2001/02 (fourth cycle). The main outcome measures were six to seven and a half year mortality and prevalence of chronic diseases.

**Results** Men with high salivary morning cortisol had a higher mortality risk than men with low levels (HR=1.63,  $p=0.04$  for the third versus the lowest tertile). Women with high salivary evening cortisol had a higher mortality risk than women with low levels (HR=1.82,  $p=0.04$  for the third versus the lowest tertile). In men, high serum cortisol was independently associated with chronic non-specific lung disease (CNSLD, OR=0.72,  $p<0.01$ ), hypertension (OR=1.38,  $p<0.01$ ), and diabetes mellitus (OR=1.38,  $p=0.02$ ). In women, high salivary evening cortisol was independently associated with diabetes mellitus (OR=1.33,  $p=0.01$ ) and CNSLD (OR=0.58,  $p=0.02$ ). No independent associations between cortisol and number of chronic diseases were found.

**Conclusion** High salivary cortisol levels were associated with increased mortality risk in a general older population. In addition, high cortisol levels were associated with higher risks of hypertension and diabetes mellitus, and lower risk of CNSLD.

## Introduction

Cortisol has an important effect on the glucose, protein, and fat metabolism and cardiovascular reactivity.<sup>1,2</sup> Also, it facilitates the body's response to stress and regulates the immune system. High cortisol level, as seen in Cushing's syndrome and corticosteroid therapy, have been associated with muscle weakness, osteoporosis, hypertension, diabetes mellitus (DM), and susceptibility to infections.<sup>3-6</sup> Some studies have shown associations between high levels of cortisol and decreased physical function.<sup>7-9</sup> Few studies investigated the relationship between cortisol and mortality in different populations. However, the results were inconsistent. Some studies concluded that high cortisol levels were associated with increased mortality in acute illnesses, whereas other studies concluded that both high and low levels of cortisol were associated with increased mortality.<sup>1,10-12</sup> Whether relationships exist between cortisol and mortality in a general older population is not yet known.

Chronic rise of cortisol levels has been associated with the pathogenesis of several disorders such as immunosuppression, obesity, cardiovascular disease, DM, stroke, and osteoporosis.<sup>13-17</sup> Also, several chronic diseases, such as DM, auto-immune diseases, rheumatoid arthritis (RA), and asthma are independently associated with cortisol level.<sup>17,18</sup> Moreover, exogenous corticosteroids are known to improve airway mucosal blood flow and are being used in the treatment of COPD and asthma.<sup>19-22</sup> However, the results were inconsistent, given that both positive and negative associations with chronic diseases have been found.<sup>17,18,23</sup>

This study aimed to examine whether high cortisol levels were associated with higher mortality rates and higher prevalences of chronic diseases in community-dwelling older persons.

## Methods

### *Subjects*

Subjects were selected from the Longitudinal Aging Study Amsterdam (LASA), an ongoing multidisciplinary cohort study on predictors and consequences of changes in physical, cognitive, emotional, and social function in older persons. Data collection and sampling procedures have been explained in more detail elsewhere.<sup>24</sup> Once in three years subjects participate in a main interview and a medical interview. The current study was done using data from participants in the second cycle in 1995/96 and in the fourth cycle in 2001/02. Figure 1 shows the design of the study sample.

Second cycle: In this cycle, serum cortisol level, mortality, and number of chronic diseases were measured. Subjects were aged 65 years and older as of January 1, 1996. Participants with available data on serum cortisol were selected (n=1279). Subjects using oral glucocorticoids, mineralocorticoids or sex hormones were excluded (n=46). Also, subjects with missing values

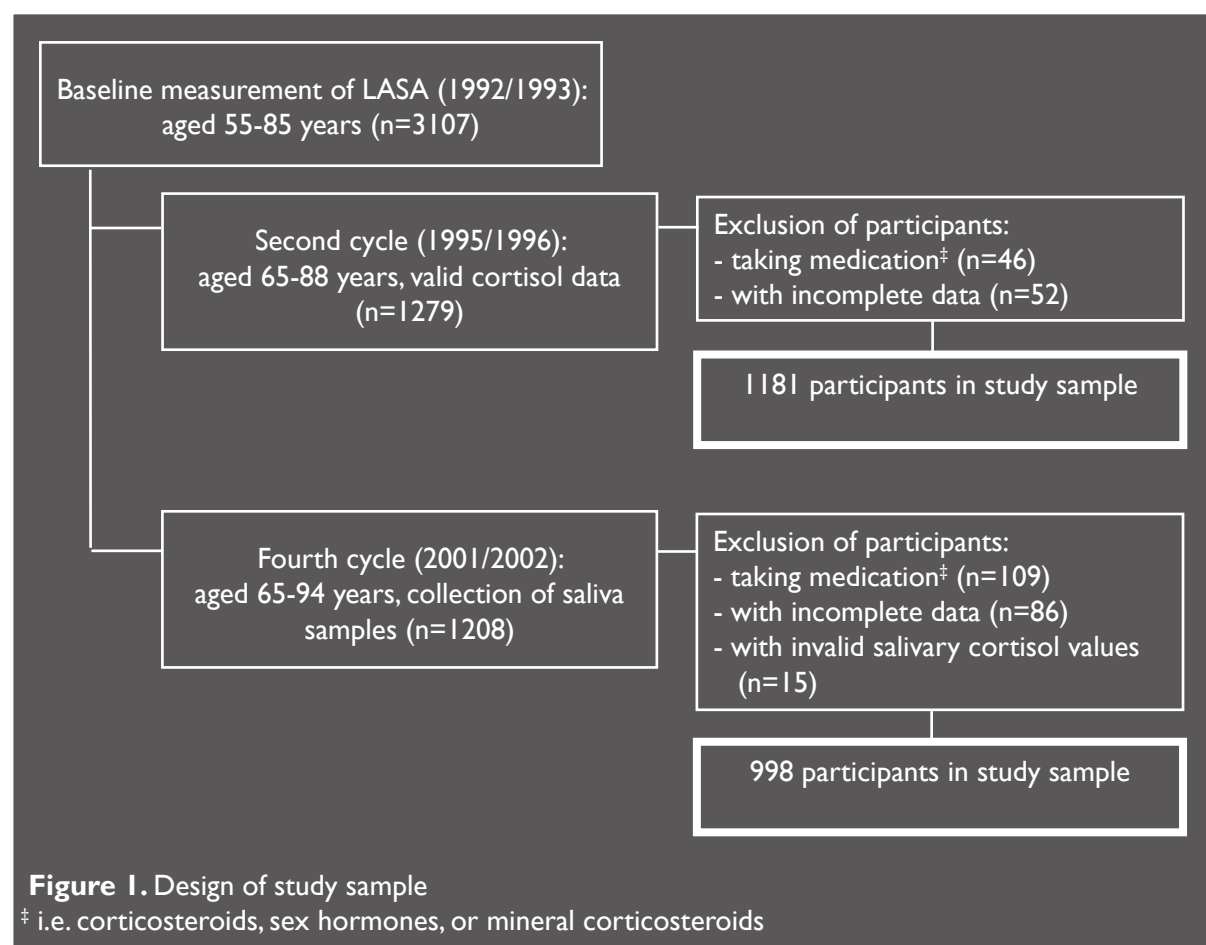
on the confounders were excluded (n=52). The number of participants included in the analyses was 1181 of whom 600 were female and 581 were male.

Fourth cycle: In this cycle, morning and evening salivary cortisol level and number of chronic diseases were measured. Subjects were aged 65 years and older as of January 1, 2002. Participants with valid salivary cortisol values and with information on chronic diseases were selected (n=1208). Subjects using oral corticosteroid, mineral corticoids or sex hormones were excluded (n=109). Also, subjects with missing values on the confounders were excluded (n=86). Subjects with morning salivary cortisol level over 100 nmol/l and evening salivary cortisol level over 30 nmol/l were considered outliers and excluded (n=15). The number of participants included in the analyses was 998 of whom 524 were female and 474 were male. Serum creatinine and albumin were not measured in this cycle. Of the participants in the second cycle, 701 (59.4 %) were also included in the fourth cycle.

#### Measurements

##### *Serum total cortisol, corticosteroid binding globulin (CBG), and serum free cortisol*

Subjects were invited to a health care centre near their homes where blood samples were taken in the morning. Most participants had their blood samples taken between 8.00 am and 10.00



am. Subjects were allowed to take tea and toast before, but no dairy products. The blood samples were centrifuged and serum was stored at -70°C until processing in 2002/2003. The serum total cortisol levels were determined using a competitive immunoassay (ACS: centauer, Bayer Diagnostics, the Netherlands). The lower limit for accurate detection of serum total cortisol was 30 nmol/l (1.0 µg/dl is 27.6 nmol/l) and the inter-assay coefficients of variations (CV) were 6 % at 150 nmol/l and 8 % at 1000 nmol/l.

Corticosteroid binding globulin level was determined using a radio-immunoassay (Medgenix Diagnostics, Belgium). The lower limit for accurate detection of CBG concentrations was 11 mg/l and the inter-assay CV's were 8 % at 30 mg/l and 5 % at 110 mg/l. Serum free cortisol was computed according to the Free Cortisol Index: serum total cortisol (nmol/l) divided by CBG (mg/l).<sup>25</sup> In none of the samples the concentrations of serum total cortisol or CBG fell below the lower detection limits.

#### *Salivary cortisol*

Saliva samples were collected using cotton balls. Subjects were instructed to rinse their mouth with water and wait ten minutes before chewing on the cotton ball. Subjects were instructed to prevent bleeding of the gum before and during the saliva collection. The cotton balls were chewed on within 30 minutes after awaking and at approximately 23.00h for around 1.5 minutes and then put in a tube. Samples were kept refrigerated until analysis. Radioimmunoassay coated tubes (Spectra Orion Diagnostics, Finland) were used to assess evening salivary cortisol. The lower detection limit was 1.38 nmol/l. In none of the samples the concentrations of salivary cortisol fell below the lower detection limit. The intra- and inter-assay CV were less than 19 %.

#### *Mortality*

Mortality information was collected from municipal registers for all subjects. The maximum survival was 7.5 years for subjects in the second cycle and 6 years for subjects in the fourth cycle. Survival (in years) was computed as the year of death minus the year of the medical interview, or when the subject was still alive, the end of follow-up minus the year of the medical interview.

#### *Chronic diseases*

The number of chronic diseases was assessed with a questionnaire. The occurrence of chronic non-specific lung disease (CNSLD: including asthma and COPD<sup>26</sup>), diabetes mellitus (DM), cancer, heart disease, peripheral arterial disease, hypertension, arthritis (both rheumatoid arthritis (RA) and osteoarthritis), and stroke were included in the analysis. The incidence of 4, 5, 6, or 7 chronic diseases was low. Therefore, number of chronic diseases was divided into four categories (i.e. no chronic diseases, 1, 2, and 3 or more chronic diseases).

*Potential effect modifiers*

Several studies found gender differences in cortisol level.<sup>27-29</sup> Also, one study found different relationships between cortisol and physical performance in male and female subjects.<sup>9</sup> Furthermore, sex differences were found in both the basal activity of the hypothalamic-pituitary-adrenal (HPA) axis<sup>29</sup> and the response of the HPA-axis to challenge.<sup>28</sup> Therefore, gender was considered a potential effect modifier.

*Potential confounders*

Body mass index (BMI) was computed from body height, measured using a stadiometer, and body weight, using a calibrated balance beam scale without upper clothing and shoes. Smoking (current smoker, yes/no) was assessed with a questionnaire and serum creatinine was measured in blood samples. Cognitive impairment was examined using the Mini Mental State Examination (MMSE); an 11-item survey which measures cognitive function (range 0-30). Scores lower than 24 indicate impaired cognitive function.<sup>30</sup> Depressive symptoms were evaluated with the Centre for Epidemiologic Studies-Depression scale (CES-D). This is a 20-item self-report scale which measures depressive symptoms. The score ranges from 0-60 and a score of 16 and higher indicates presence of clinically relevant depressive symptoms.<sup>31</sup> Alcohol consumption was categorized according to the alcohol consumption index adapted from the Garretsen alcohol index.<sup>32</sup> The adapted index was based on days of drinking per week, categorized as no alcohol use, light (maximum of 6 drinks per week), moderate (7-21 drinks per week), excessive (22-35 drinks per week) and very excessive (more than 35 drinks per week).

*Statistical analyses*

All analyses were conducted using SPSS software. Three different models were used. First, the Cox proportional hazard model was conducted to examine the association between cortisol level and mortality rate. Second, logistic regression was conducted to investigate the association between cortisol and individual chronic diseases. Third, the ordinal regression analysis was used to examine the association between cortisol level and number of chronic diseases. Possible effect modifiers were evaluated by entering the product of the effect modifier and continuous cortisol values into the regression model. Effect modifiers were considered to be significant at a p-value smaller than 0.10. The individual variables were analyzed for linearity using two methods. First, cortisol and cortisol-squared were added to the model. Second, cortisol was added to the model in dummies. If the squared term was significant ( $p < 0.10$ ) or the regression coefficients of the dummies did not increase or decrease linearly, the association was considered non-linear. Variables, which led to an important change in the regression coefficient of the association between cortisol and the outcome variables, were included as confounders. The variables, which influenced the regression coefficient the most, were selected. P-values were based on two-sided tests and were considered statistically significant at a p-value smaller than 0.05.

## Results

In the second cycle (1995/96), the mean age of the subjects was 75.1 years (SD =6.5) in women and 75.4 years (SD=6.5) in men (Table 1). The mean serum total cortisol level was 480.5 nmol/l (SD=176.2) in women and 517.7 nmol/l (SD=161.7) in men. The mean serum free cortisol level was 10.9 (SD=4.2) in women and 14.0 (SD=4.4) in men. Excluded subjects were more often female ( $p<0.01$ ), used less alcohol ( $p<0.01$ ), were older ( $p=0.02$ ), and more depressed ( $p<0.01$ ). In the fourth cycle (2001/02), the mean age of the subjects was 75.1 years (SD=6.8) in women and 74.9 years (SD=6.9) in men. The mean morning salivary cortisol level was 17.1 nmol/l (SD=20.3) in women and 18.2 nmol/l (SD=30.2) in men. The median evening salivary cortisol level was 2.9 nmol/l (IQR=2.1-3.9) in women and 2.8 nmol/l (IQR=2.1-4.1) in men. Excluded subjects had higher morning ( $p<0.01$ ) and evening salivary cortisol level ( $p=0.02$ ), had more chronic diseases ( $p=0.02$ ), and were younger ( $p<0.01$ ).

**Table 1.** Baseline characteristics

	Second cycle		Fourth cycle	
	Women (n=600)	Men (n=581)	Women (n=524)	Men (n=474)
Age <sup>†</sup>	75.1 (6.5)	75.4 (6.5)	75.1 (6.8)	74.9 (6.9)
Body Mass Index <sup>†</sup>	27.6 (4.6)	26.1 (3.3)	28.0 (4.8)	26.8 (3.3)
Survival (years) <sup>‡</sup>	6.8 [6.4-7.1]	6.7 [4.9-7.1]	6.0 [6.0-6.0]	6.0 [6.0-6.0]
Smoking (% yes)	12.5	24.3	11.1	20.1
Alcohol use (Garretsen index) <sup>‡</sup>	1 [0-1]	1 [1-2]	1 [1-1]	1 [1-2]
Depression (CES-D) <sup>‡</sup>	8 [3-14]	4 [2-9]	8 [4-13]	6 [3-11]
Cognitive functioning (MMSE) <sup>‡</sup>	28 [26-29]	428 [26-29]	28 [26-29]	28 [26-29]
Serum creatinine (μmol/l) <sup>†</sup>	85.2 (33.2)	106.1 (37.3)	-	-
Number of chronic diseases <sup>‡</sup>	1 [0-1]	1 [0-1]	1 [1-2]	1 [0-2]
Serum total cortisol <sup>†‡</sup>	480.5 (176.2)	517.7 (161.7)	-	-
Serum free cortisol <sup>†</sup>	10.9 (4.2)	14.0 (4.4)	-	-
Morning salivary cortisol <sup>†‡</sup>	-	-	17.1 (20.3)	18.2 (30.2)
Evening salivary cortisol <sup>†‡</sup>	-	-	2.9 [2.1-3.9]	2.8 [2.1-4.1]
Diabetes Mellitus (% yes)	8.2	6.4	9.5	9.5
CNSLD (% yes)	11.2	16.4	10.9	15.4
Rheumatoid arthritis (% yes)	13.3	6.0	11.8	5.9
Osteoarthritis (% yes)	11.7	4.6	57.1	35.2
Stroke (% yes)	5.3	8.4	4.6	9.5
Hypertension (% yes)	26.7	17.7	36.3	26.4
Heart disease (% yes)	19.3	32.4	23.7	34.4
Arterial disease (% yes)	9.7	11.7	8.0	12.7
Cancer (% yes)	11.8	10.2	16.6	12.0

<sup>†</sup> Means (Standard Deviation); <sup>‡</sup> Median [Interquartile range]; <sup>#</sup> cortisol was presented in nmol/l; CNSLD Chronic Non-Specific Lung Disease



*Relationship between cortisol and mortality*

Within 7.5 years after baseline in 1995/95, 147 women (25 %) and 219 men (38 %) died. Gender was found to be an effect modifier in the association between cortisol and mortality ( $p < 0.003$ ). Therefore, further analyses were stratified for gender. In the univariate model, the regression coefficients did not increase linearly in both women and men; therefore the association of serum cortisol with mortality was considered non-linear. Further analyses were done with serum cortisol values in tertiles, with the lowest tertile as the reference category. After adjustment for the confounders, no association between serum cortisol and mortality was found in both genders (Table 2). Within 6 years after baseline in 2001/02, 72 women (14 %) and 105 men (22 %) died. In men, a higher mortality risk was found in the third versus the lowest tertile for salivary morning cortisol ( $HR = 1.63$ ,  $p = 0.04$ ). In women, a higher mortality risk was found in the third versus the lowest tertile for salivary evening cortisol ( $HR = 1.82$ ,  $p = 0.04$ ).

*Relationship between cortisol and chronic diseases*

Gender was found to be an effect modifier in the second cycle for serum free cortisol ( $p = 0.08$ ) and in the fourth cycle for both salivary cortisol measures ( $p < 0.07$ ). Gender was not an effect modifier in the second cycle for serum total cortisol ( $p = 0.11$ ). To enhance comparability all analyses were stratified for gender. The associations between serum cortisol, salivary cortisol, and number of chronic disease did not ascend linearly. Therefore, serum and salivary cortisol level were included in the model in quartiles. The lowest quartile was the reference quartile.

In the second cycle, men with high serum total cortisol levels had a significantly higher risk of hypertension ( $OR = 1.38$ ,  $p = 0.001$ ) and DM ( $OR = 1.38$ ,  $p = 0.02$ ) and tended to have a higher risk of heart disease ( $OR = 1.17$ ,  $p = 0.08$ ) (ORs are presented for a 1 SD higher cortisol level, Table 3). A trend for a higher risk was found for serum free cortisol and hypertension ( $OR = 1.21$ ,  $p = 0.09$ ). Men with high serum total or serum free cortisol had a significantly lower risk of CNSLD (serum total cortisol:  $OR = 0.72$ ,  $p = 0.001$ ; serum free cortisol:  $OR = 0.71$ ,  $p = 0.01$ ). In men, no associations were found between serum total and free cortisol and cancer, peripheral arterial disease, arthritis, and stroke. Women with higher serum free cortisol levels tended to have a higher risk of rheumatoid arthritis ( $OR = 0.80$ ,  $p = 0.09$ ). In women, no associations were found for serum cortisol and the remaining diseases (data not shown).

In the fourth cycle, men with higher morning salivary cortisol levels had a lower risk of CNSLD ( $OR = 0.72$ ,  $p = 0.03$ ) (ORs are presented for a 1 SD higher cortisol level, Table 3). Men with higher evening salivary cortisol levels also tended to have a lower risk of CNSLD ( $OR = 0.73$ ,  $p = 0.07$ ). Furthermore, men with higher salivary evening cortisol tended to have a higher risk of DM ( $OR = 1.27$ ,  $p = 0.06$ ). In women, higher salivary evening cortisol was associated with a higher risk of DM ( $OR = 1.33$ ,  $p = 0.01$ ). In addition, women with higher salivary morning cortisol tended to



**Table 2.** Relationship between serum cortisol, salivary evening cortisol and mortality in men and women (second and fourth cycle)

	Women			Men		
	Deceased n (%)	HR	p-value	Deceased n (%)	HR	p-value
Serum total cortisol						
T1	44 (21.7)	1.00		71 (36.2)	1.00	
T2	40 (20.2)	0.92	0.70	70 (35.9)	1.00	0.98
T3	63 (31.7)	1.48	0.05	78 (41.1)	1.17	0.33
adjusted <sup>‡</sup>						
T1	44 (21.7)	1.00		71 (36.2)	1.00	
T2	40 (20.2)	0.91	0.67	70 (35.9)	0.97	0.86
T3	63 (31.7)	1.26	0.25	78 (41.1)	1.19	0.29
Serum free cortisol						
T1	38 (18.9)	1.00		71 (36.8)	1.00	
T2	49 (24.6)	1.33	0.19	70 (36.1)	0.95	0.75
T3	60 (30.0)	1.63	0.02	78 (40.2)	1.14	0.41
adjusted <sup>‡</sup>						
T1	38 (18.9)	1.00		71 (36.8)	1.00	
T2	49 (24.6)	0.94	0.79	70 (36.1)	0.80	0.20
T3	60 (30.0)	1.04	0.86	78 (40.2)	0.98	0.88
Morning salivary cortisol						
T1	27 (15.6)	1.00		32 (20.3)	1.00	
T2	28 (16.9)	1.09	0.76	31 (19.0)	0.98	0.93
T3	19 (10.3)	0.64	0.13	45 (29.4)	1.63	0.04
adjusted <sup>†</sup>						
T1	27 (15.6)	1.00		32 (20.3)	1.00	
T2	28 (16.9)	1.18	0.55	31 (19.0)	0.98	0.93
T3	19 (10.3)	0.65	0.16	45 (29.4)	1.63	0.04
Evening salivary cortisol						
T1	18 (10.2)	1.00		24 (16.1)	1.00	
T2	16 (9.1)	0.90	0.75	39 (25.0)	1.61	0.06
T3	40 (23.3)	2.49	0.001	44 (27.0)	1.84	0.02
adjusted <sup>†</sup>						
T1	18 (10.2)	1.00		24 (16.1)	1.00	
T2	16 (9.1)	0.76	0.42	39 (25.0)	1.41	0.18
T3	40 (23.3)	1.82	0.04	44 (27.0)	1.35	0.24

Hazard Ratios (HR) and p-values are presented unadjusted and after adjustment for <sup>‡</sup> age, albumin, number of chronic diseases, and MMSE in women, and for age, albumin, creatinine, and smoking in men; <sup>†</sup> age, number of chronic diseases, and MMSE in women, and for age and smoking in men. Cut-off values for the cortisol tertiles were: serum total cortisol: 388 and 530 nmol/l in women and 437 and 575 nmol/l in men; serum free cortisol: 8.5 and 12.2 in women and 11.8 and 15.6 in men; morning salivary cortisol: 11.5 and 17.0 nmol/l in women and 11.0 and 16.0 nmol/l in men; evening salivary cortisol: 2.3 and 3.4 nmol/l in both men and women.

have a higher risk of hypertension (OR=0.85,  $p=0.09$ ). Both in women and men, no associations were found between salivary cortisol and cancer, heart disease, peripheral arterial disease, arthritis, or stroke (data not shown).

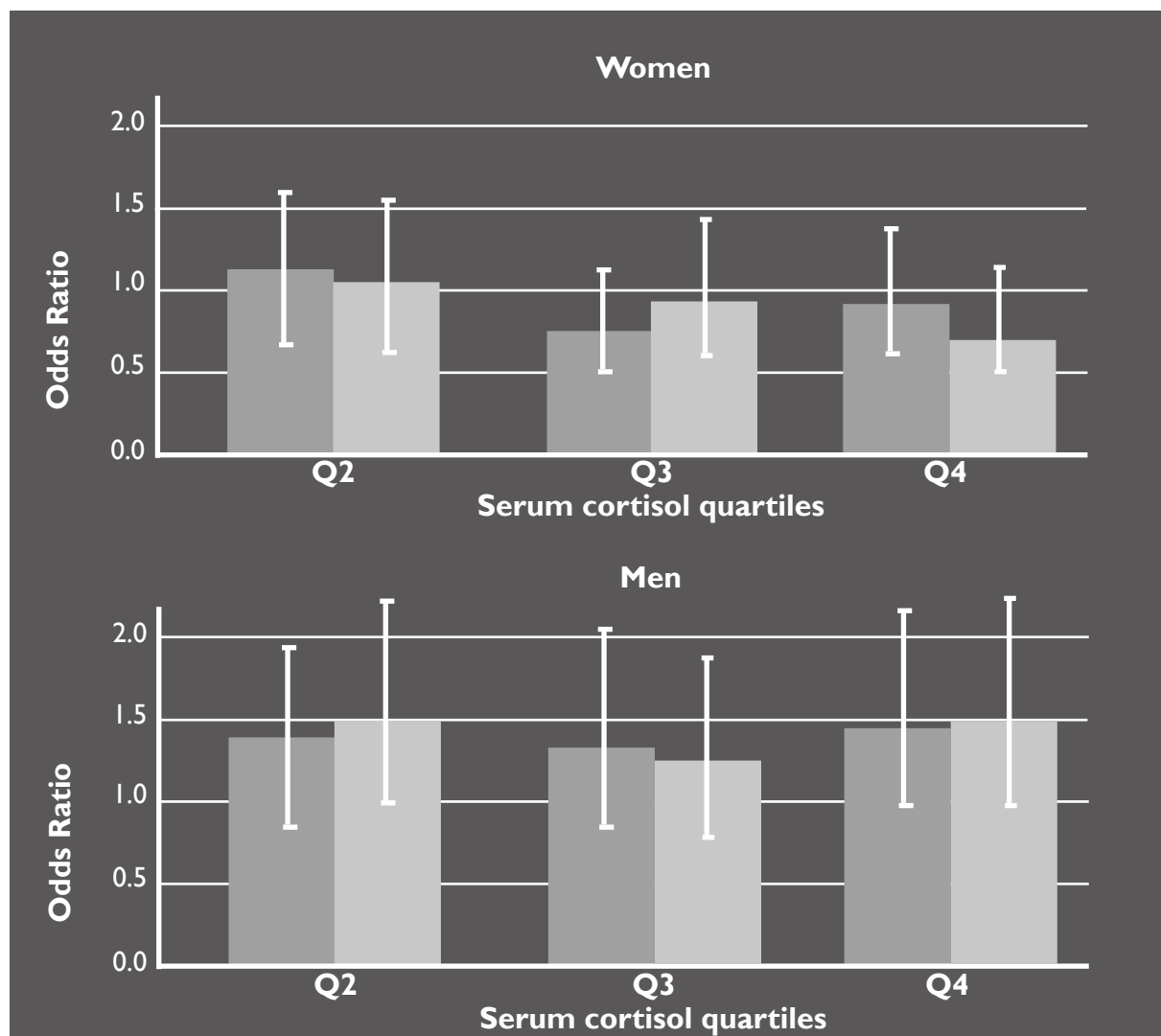
Since higher cortisol levels were associated with lower risks of CNSLD and higher risks of other chronic diseases, CNSLD was not included in the variable number of chronic diseases. In the second cycle, in men, the adjusted associations for serum free cortisol and number of chronic diseases showed a tendency towards a higher risk of more chronic diseases in the second and fourth quartile as compared with the lowest quartile (2nd quartile: OR=1.50,  $p=0.06$ ; 4th quartile: OR=1.51,  $p=0.07$ ). After adjustment for the confounders, the association of serum total cortisol and number of chronic diseases showed a tendency towards a higher risk of more chronic diseases in the fourth quartile (OR=1.47,  $p=0.08$ ) (Figure 2). In women, no associations were found between serum cortisol and number of chronic diseases.

**Table 3.** Relationships between cortisol and chronic diseases in men and women

	Women		Men	
	OR	p-value	OR	p-value
<b>Heart disease</b>				
serum total cortisol	1.18	0.12	1.17	0.08
serum free cortisol	1.09	0.40	1.09	0.34
salivary morning cortisol	1.01	0.92	0.94	0.49
salivary evening cortisol	1.11	0.28	0.95	0.58
<b>Diabetes Mellitus</b>				
serum total cortisol	1.10	0.51	1.38	0.02
serum free cortisol	0.93	0.64	1.12	0.53
salivary morning cortisol	0.86	0.35	1.14	0.42
salivary evening cortisol	1.33	0.01	1.27	0.06
<b>Hypertension</b>				
serum total cortisol	1.07	0.49	1.38	0.001
serum free cortisol	1.11	0.30	1.21	0.09
salivary morning cortisol	0.85	0.09	1.14	0.21
salivary evening cortisol	1.00	1.00	1.07	0.49
<b>Chronic Non-Specific Lung Disease</b>				
serum total cortisol	0.99	0.49	0.72	0.001
serum free cortisol	0.90	0.46	0.71	0.01
salivary morning cortisol	0.94	0.64	0.72	0.03
salivary evening cortisol	0.58	0.02	0.73	0.07

Odds Ratios (OR), expressed per standard deviation higher cortisol level, and p-values are presented for the (near) significant associations after adjustment for age, BMI, depression, alcohol use, and in the second cycle for serum creatinine.

In the fourth cycle, in women, a lower risk for more chronic diseases was found for the second quartile as compared with the lowest quartile of salivary morning cortisol ( $OR=0.58$ ,  $p=0.02$ ). In women, no independent associations of evening salivary cortisol and number of chronic diseases were found. In men, no independent associations were found for morning and evening salivary cortisol and number of chronic diseases (data not shown).



**Figure 2.** Relationship between serum cortisol level and the risk for a higher number of chronic diseases expressed in odds ratios in men and women. Odds Ratios and 95 % confidence intervals are presented for both women (upper panel) and men (lower panel) and for both serum total cortisol (dark gray bars) and serum free cortisol (light gray bars) after adjustment for age, BMI, serum creatinine, alcohol use, and depression. The lowest cortisol quartiles were the reference quartiles with an odds ratio of 1.

## Discussion

The current study explored the associations between cortisol level, mortality, and prevalence of chronic diseases in community-dwelling older persons in the Netherlands. The data suggest some interesting points. First, a high salivary cortisol level was independently associated with an increased mortality risk. Second, a high serum cortisol level was independently associated with higher risks of hypertension and diabetes mellitus type II, and a lower risk of chronic non-specific lung disease. Third, a high salivary cortisol level was independently associated with a higher risk of diabetes mellitus type II. Fourth, both serum and salivary cortisol level were not independently associated with number of chronic diseases.

### *Cortisol and mortality*

In the current study, persons with high salivary cortisol levels had higher mortality risks. These associations remained significant after adjustment for chronic diseases. Thus, chronic diseases did not fully explain the association between cortisol and mortality. However, previous studies found that high cortisol levels were associated with an increased mortality risk in hospital admitted patients, acute stroke patients and resuscitated patients after cardiopulmonary arrest.<sup>10-12</sup> Acute illnesses were not measured in the current study. It may be that the association between a high level of cortisol and mortality is explained by acute illnesses.

The allostatic load model suggests that a set of ten biomarkers, including cortisol level, predicts mortality.<sup>33</sup> Improvement of these biomarkers may reduce the mortality risk.<sup>34</sup> In these studies the individual biomarkers were not associated whereas the complete set of biomarkers was associated with higher mortality.<sup>33,34</sup> We found associations with mortality for some of the cortisol measures, but not with all cortisol measures. The independent relationship between cortisol and mortality may not be very strong. Further research should focus on the role of cortisol in relationship with mortality within the context of other biomarkers.

### *Cortisol and chronic diseases*

This is the first study that examined the association between cortisol and number of chronic diseases. Although no independent association between cortisol and the number of chronic diseases was found, there may be a tendency towards an increased number of chronic diseases in men with high serum cortisol levels. Moreover, we did find associations between cortisol and some of the individual chronic diseases.

Two studies examined the relationship between cortisol and blood pressure in healthy adults<sup>35</sup> and in healthy older men<sup>36</sup> and found that blood pressure increased with higher serum cortisol levels. Our findings in men were in line with these studies, although no associations were found in women. To our knowledge, gender differences in the relationship between cortisol and

hypertension were not studied before. However, some studies found gender differences in HPA-axis reactivity and variability, yet, the results were inconsistent.<sup>28,37</sup> Further research is necessary to explain the gender differences in the relationship between cortisol and hypertension.

Previous studies reported that fasting glucose level and insulin resistance increased with higher cortisol levels.<sup>35,36</sup> These studies examined indicators of diabetes mellitus, while the current study measured the actual disease. As expected, high levels of cortisol were associated with diabetes mellitus. The association between cortisol and diabetes mellitus (and hypertension) may be confounded by obesity. We did adjust for BMI, but waist circumference may be a better measure for obesity. Yet, the correlation between BMI and waist circumference was high ( $r=0.74$ ,  $p<0.001$ ), and therefore the two confounders should not be included in the model together. Using the 10 % rule, both waist circumference and BMI were equally important confounders and thus it did not matter for the results which of the two confounders was included.

The foetal programming hypothesis suggests that programming of the HPA-axis is the link between reduced fetal growth and poor health in later life.<sup>38-40</sup> Poor fetal growth has been associated with metabolic syndrome and cardiovascular disease in adults.<sup>18,23,36,41,42</sup> In addition, associations have been found between intrauterine growth restriction and both hypo- and hypercortisolism.<sup>43</sup> In line with this theory, older persons with high levels of cortisol had higher risks of diabetes mellitus and hypertension, and lower risks of chronic non-specific lung disease.

In the current study, a high cortisol level appeared to protect against CNSLD. To our knowledge, no study has examined the relationship between endogenous cortisol level and CNSLD before. First, this association may be due to a survivor effect: persons with chronic non-specific lung diseases may have died at younger ages. If this were the explanation, different associations would be expected for younger and older age groups. An age-interaction ( $p<0.10$ ) was observed in only one of the eight models (i.e. in women and with free cortisol), and was probably due to chance. Thus, a survivor effect is unlikely to explain the protective effect of cortisol on CNSLD. Second, corticosteroids are being used in the treatment of COPD and asthma by improving airway mucosal blood flow.<sup>19-22</sup> CNSLD is based on an inflammatory reaction. The current results suggest that not only exogenous cortisol, but also endogenous cortisol may have an immunosuppressant effect on inflammation in the airway mucosa.

Strengths of the current study are its large sample size and prospective design. Furthermore, the LASA sample is representative for the community-dwelling older population in the Netherlands.<sup>44</sup> A few limitations need to be discussed. First, serum cortisol was measured only once in the second cycle, while the cortisol level is known to oscillate during the day and with stress. The diurnal pattern of cortisol is influenced by many factors, especially during

the morning peak.<sup>45</sup> Morning levels reflect HPA-axis reactivity whereas evening levels reflect the basal level, but both levels may contribute to the understanding of the role of cortisol in health and disease. In order to examine the long term effects of cortisol, the basal level may be the most reliable measure. Furthermore, salivary cortisol is less susceptible to the fluctuations than serum cortisol. Therefore, late evening salivary cortisol may be a better measure for basal cortisol levels.<sup>45</sup> We used both serum and salivary measures of cortisol to test the robustness of our findings. Although per disease the associations were not significant for all cortisol measures, the associations pointed in the same direction. Future research is necessary to confirm these associations. Second, serum free cortisol was calculated using the Free Cortisol Index (i.e. cortisol/CBG),<sup>25</sup> which is an estimate of the actual free cortisol concentration. At higher cortisol/CBG ratio's, cortisol levels exceed CBG binding capacity, and then free cortisol rises steeply. Calculating free cortisol using an algorithm based on the law of mass action, with CBG and albumin as the binding proteins and the dissociation constants as described by Lentjes et al. (1999)<sup>46</sup> takes this phenomenon into account. However, the correlation between the Free Cortisol Index and algorithm-based free cortisol was high ( $r > 0.95$ ,  $p < 0.001$ ), indicating that the Free Cortisol Index provides a good estimate of the true free cortisol concentration in this population. Third, some chronic diseases, such as stroke and peripheral arterial disease had low prevalences (<10 %). Maybe, no associations were found for these diseases due to limited power. In addition, prevalence of chronic diseases was based on self-report. However, self-report was found to be valid after comparison with general practitioners information.<sup>47</sup> Fourth, the observed significant associations may be caused by multiple testing. However, the results found are biologically plausible. Moreover, if a stricter  $\alpha$  of 0.01 is used, some associations remain significant.

In conclusion, the results suggest that high salivary cortisol levels are associated with an increased mortality risk in a general older population. In addition, a high cortisol level is associated with a higher risk of hypertension, and diabetes mellitus and a lower risk of chronic non-specific lung disease.

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# 5

**Is there a U-shaped association between physical activity and falling  
in community-dwelling older persons?**

Submitted as: GMEE Peeters, NM van Schoor, SMF Pluijm, DJH Deeg, P Lips. Is there a U-shaped association between physical activity and falling in community-dwelling older persons?

Opmerking van deelnemer op het fractuurblad: "Ik ben van nature nogal slordig met lopen en fietsen waardoor ik struikel of val, maar ik kan goed botbreuken voorkomen."

## Abstract

**Objective** Previous studies suggest that the relationship between physical activity and falling may be U-shaped. This study tests this hypothesis, and examines whether this relationship is modified by level of physical functioning.

**Methods** Community-dwelling persons (65+) from the Longitudinal Aging Study Amsterdam (LASA) were prospectively followed on falls for three years after baseline assessment in 1995/96 (n=1337). Outcome measures were time to first fall and time to recurrent falling (i.e. time to second fall within a 6-month period). The LASA Physical Activity Questionnaire was used to calculate physical activity in minutes per day weighted for intensity (range 0-2000). Physical functioning was measured with physical performance tests and self reported functional limitations.

**Results** No evidence for a non-linear association was found ( $p$  for physical activity<sup>2</sup>>0.20). No significant association was found between physical activity and time to first fall. An increase in physical activity of 100 units led to a 4 % decrease in risk of recurrent falling (adjusted Hazard Ratio: 0.96, 95 % Confidence Interval: 0.92-0.99). No interactions with physical performance or functional limitations were found ( $p$ >0.50).

**Conclusions** The hypothesized U-shaped relationship between physical activity and falling could not be confirmed. At higher levels of physical activity, the risk of recurrent falling decreased, while no association was found with fall risk. Moreover, the associations did not seem to be modified by level of physical functioning.

## Introduction

Falling is a major cause of injury and disablement in older persons. About 30 % of older community-dwelling persons falls once a year and 15 % falls at least twice a year.<sup>1,2</sup> The consequences of falling vary from fear of falling and soft tissue injuries to (hip) fractures and increased mortality.<sup>2-5</sup>

Physical (in)activity has been identified as an important risk factor of falling in older persons.<sup>6-8</sup> Both low and high levels of physical activity have been associated with an increased fall risk.<sup>6,9-12</sup> Inactivity may lead to muscle weakness and slow neuromuscular reactions,<sup>7</sup> whereas highly active persons are more often exposed to hazardous situations.<sup>7,11</sup> Current clinical guidelines and health care policies recommend physical activity among older persons because of its beneficial effects on many health outcomes, such as cardiovascular functioning and bone quality. e.g. <sup>13,14</sup> If there is indeed a U-shaped relationship, falling may be an adverse effect of these recommendations and it may be necessary to reconsider these guidelines and policies.

To our knowledge, only three studies examined the relationship between physical activity and falls, with physical activity in three or more categories and thus giving insight in the shape of the relationship.<sup>10-12</sup> However, none of the studies tested the shape of the relationship using correct statistical techniques. Moreover, none of these studies used a validated physical activity questionnaire in combination with prospectively measured falls in a general population of community-dwelling older persons. The current study overcomes the limitations of previous studies.

The relationship between physical activity and falling may differ for well and poor functioning persons. Active older persons may have an increased fall risk due to an incongruence of what they are able to do and what they actually do.<sup>15</sup> Interactions with physical activity and both leg extension power<sup>10</sup> and use of a walking aid<sup>11</sup> have been found in association with (recurrent) falling. Both leg power and use of a walking aid are indicators of physical functioning, but do not measure the entire concept. Physical functioning can be measured more validly by physical performance tests (objective measure of what one can do in a test situation) and functional limitations (subjective measure of what one can do in real-life situations).<sup>16</sup>

In the literature a distinction is made between occasional fallers and recurrent fallers.<sup>17,18</sup> A single fall may be coincidental and may be caused mainly by environmental factors, whereas recurrent falls are usually caused by physical, cognitive and behavioural factors within the person.<sup>19</sup> Physical activity may be associated differently with falling and recurrent falling.

This study examined the relationship between physical activity and time to first fall and time to recurrent falling in community-dwelling older persons. We hypothesized that the relationship between physical activity and (recurrent) falling would be U-shaped: both low and high levels of physical activity were expected to be associated with an increased fall risk. Also, we expected that highly active older persons with poor physical functioning had the highest risk of falling.

## Methods

### *Subjects*

This study was performed within the Longitudinal Aging Study Amsterdam (LASA), an ongoing interdisciplinary cohort study on predictors and consequences of changes in physical, cognitive, emotional, and social functioning in older persons.<sup>20</sup> A random sample of older men and women stratified for age, sex, and expected five-year mortality was drawn from the population registries of eleven municipalities in the west, northeast, and south of the Netherlands. The sampling and data collection procedures have been described in detail elsewhere.<sup>20,21</sup> The sample for this study consisted of 1509 participants in the second cycle (1995/1996) who were 65 years or older as of January 1, 1996. In total, 1427 participants had complete fall follow-up, of whom 1342 participants had complete data (54 participants had missing values on physical activity and a further 31 on any of the confounders). Five additional participants were considered outliers and excluded from the analysis because of unlikely high values for physical activity (i.e. >11.5 hours of activity per day or >2000 min/day x MET). In total, 1337 participants were included in the analysis. The Medical Ethics Committee approved the study and all participants signed informed consent.

### *Falls and recurrent falling*

Falls were prospectively assessed during three years following the baseline interview in 1995/1996 using a fall calendar.<sup>22</sup> Participants were asked to tick every week whether or not they had fallen. Once every 3 months the calendar page was mailed to the institute. If the calendar procedure was too complicated, if the page was not received (even after a reminder), or if the page was completed incorrectly, the participants were contacted per telephone. Proxies were contacted if participants were unable to respond. A fall was defined as “an unintentional change in position resulting in coming to rest at a lower level or on the ground”.<sup>23</sup> Recurrent falling was defined as “falling at least two times within six months during the three-year fall follow-up”.<sup>24</sup> An occasional faller was defined as a person who fell at least once during follow-up, but who did not meet the criteria for recurrent falling. Time from baseline to the date of the first fall was determined as time to first fall; time from baseline to the date of the second fall within a six-month period was determined as the time to recurrent falling. Participants who were deceased, could not be contacted or refused further participation during follow-up were included in the analyses until time of drop-out.

*Physical activity*

Physical activity was measured using the validated LASA Physical Activity Questionnaire (LAPAQ),<sup>25</sup> an interviewer-administered questionnaire which estimates the frequency and duration of participation in activities in the previous two weeks. The activities were walking, cycling, light and heavy household work and a maximum of two sports. To take the intensity of the activities into account, metabolic equivalent (MET) scores were assigned to each activity based on published MET scores lists.<sup>26,27</sup> For each activity, the frequency, duration in minutes, and MET score were multiplied and then divided by 14 days (i.e. (frequency x duration x MET)/14). The minutes spent per activity per day were summed up to a total physical activity score (minutes/day x MET). For example, a participant who walks outside for 60 minutes 4 times per 2 weeks ( $4 \times 60 \times 3.5/14=60$ ) and does light household work for 30 minutes per day ( $14 \times 30 \times 2.5/14=75$ ), has a physical activity score of 135 minutes/day weighted for intensity.

*Potential effect modifiers*

Physical functioning was measured by physical performance and functional limitations. Physical performance was measured using three standardized tests.<sup>22,28</sup> The chair stands test measures the time needed to stand up from a chair and sit down five times. The walk test measures the time needed to walk 3 meters, turn 180° and walk back. During the tandem stand the participant stands unsupported with one foot behind the other (heel against toe) up to 10 seconds with the eyes open. The scores of the chair stands and walk test were categorized into quartiles (1=slowest, 4=fastest). The score of 0 was assigned when the participant was unable to complete a test. For the tandem stand, 0 points were scored when the participant was able to hold for less than 3 seconds, 2 points for 3 to 9 seconds, and 4 points for 10 seconds. The three scores were summed (range 0-12), a score of 12 representing optimal physical performance. The score was dichotomized using the median score of 7 as the cut-off value (0-7 vs. 8-12).

Functional limitations were assessed using a validated questionnaire about the degree of difficulty (1=unable, to 5=no difficulty) with climbing stairs, walking 5 minutes outdoors without resting, getting up and sitting down in a chair, dressing and undressing oneself, cutting one's toenails and using own or public transportation.<sup>29</sup> The scores on these six items were dichotomized (0=no difficulty, 1=at least some difficulty (scores 1-4)) and summed to a total score (range 0-6). A score of 6 represents difficulties with all six activities. The total score was dichotomized using the median score of 1 as a cut-off value (0 vs.  $\geq 1$  limitations).

*Confounders*

Age and sex were derived from the municipal registries. Body Mass Index (BMI) was calculated as weight (kg)/ height (m)<sup>2</sup>. The number of chronic diseases was assessed using self-reports on chronic diseases, which included chronic non-specific lung diseases, cardiac diseases, vascular

diseases, stroke, diabetes mellitus, malignant neoplasms and joint disorders (i.e. osteoarthritis and rheumatoid arthritis) (range 0-7).<sup>30</sup> Medication use was assessed by recording the names of the medications directly from the containers. Use of psychotropic medication (antipsychotics, antidepressants, anxiolytics or hypnotics) was dichotomized as non-users versus users. Cognitive functioning was measured using the Mini Mental State Examination (MMSE, range 0-30).<sup>31</sup> Depressive symptoms were assessed using the Center for Epidemiologic Studies-Depression scale (CES-D, range 0-60). Fear of falling was measured using a modified version of the Falls Efficacy Scale (FES).<sup>32</sup> The participants reported how concerned (0=not concerned, 3=very concerned) about falling they were while carrying out 10 activities of daily living (range 0-30).

### *Statistical method*

Differences in baseline characteristics for non-fallers, occasional fallers, and recurrent fallers were tested using ANOVA for normally distributed continuous variables, the Kruskal-Wallis test for skewed continuous variables, and the Chi squared test for dichotomous variables. To examine the association between physical activity and time to first and recurrent falls, hazard ratios (HR) and 95 % confidence intervals (CI) were calculated using the Cox proportional hazards model. The analyses were performed univariate and with adjustment for age, sex, chronic diseases, BMI, MMSE, depressive symptoms, psychotropic medication and fear of falling. First, a quadratic term of physical activity (physical activity<sup>2</sup>) was included to assess a potential non-linear relationship. Second, to test effect modification by physical performance (physical activity x physical performance) and by functional limitations (physical activity x functional limitations), interaction terms were included in two separate models. No co-linearity between physical activity and physical performance or functional limitations was found ( $r < 0.21$ ). To test for non-linearity and interaction, the difference in -2 log likelihood was tested using the chi squared test ( $p < 0.10$ ). Third, if an interaction term was significant, analyses were stratified by physical performance or functional limitations. P-values were based on two-sided tests and were considered statistically significant at  $p < 0.05$ . All analyses were conducted using SPSS software (version 14.0.2).

## **Results**

As compared with responders, non-responders were older, had lower BMI, more health problems (e.g. chronic diseases and depressive symptoms), poorer cognitive functioning, higher scores for fear of falling, lower levels of physical performance, were less active ( $p$  for all characteristics  $\leq 0.01$ ), and tended to be more often recurrent fallers ( $p = 0.08$ ). In total, 1337 participants were included, of whom 167 participants (12 %) dropped out during three years of follow-up.

During three years, 740 participants (55.3 %) reported at least one fall. Table 1 shows the baseline characteristics for non-fallers ( $n = 597$ ), occasional fallers ( $n = 410$ ), and recurrent fallers ( $n = 330$ ).



The three groups clearly differ in all baseline characteristics. The median physical activity in the total sample was 459 min/day x MET (Interquartile Range=259-703).

The -2 log likelihood between the model with the linear term of physical activity and the model with both the linear term and the quadratic term of physical activity was not significant for the outcome time to first fall ( $p=0.20$ ). This indicates that there is no U-shaped association between physical activity and time to first fall. The interactions between physical activity and physical performance ( $p=0.99$ ) or functional limitations ( $p=0.99$ ) were not significant. Therefore, further analyses were not stratified for physical performance or functional limitations. The linear association between physical activity and time to first fall was not significant: the hazard ratio for an increase in physical activity of 100 units was 0.98 (CI: 0.96,-1.01) (Table 2). Adjustment for potential confounders did not change the association. Additional adjustment for physical performance or functional limitations did not change the association either (HR=0.98, CI: 0.98-1.01 for both models). In Figure 1, we modeled the association between physical activity and time to first fall. To give insight in the actual data, we also presented the hazard ratios for physical activity in categories of 400 units width against fall risk in Figure 2.

The -2 log likelihood between the model with the linear term of physical activity and the model with both the linear term and the quadratic term of physical activity was not significant for the outcome time to recurrent falling ( $p=0.82$ ). This indicates that there is no U-shaped

**Table 1.** Baseline characteristics

	Non-fallers n=597	Occasional fallers n=410	Recurrent fallers n=330	p-value
Sex (% women) <sup>‡</sup>	44.1	61.2	52.1	<0.001
Age (years) <sup>#</sup>	74.8 (6.2)	74.9 (6.4)	77.0 (6.9)	<0.001
BMI (kg/m <sup>2</sup> ) <sup>#</sup>	26.9 (4.2)	27.4 (4.5)	26.5 (4.0)	0.009
Chronic diseases (0-7) <sup>†</sup>	1 [0-2]	1 [0-2]	1 [1-2]	0.01
Psychotropic medicine (% yes) <sup>‡</sup>	10.4	16.3	20.6	<0.001
MMSE (0-30) <sup>†</sup>	28 [26-29]	28 [26-29]	27 [25-29]	0.04
Depressive symptoms (0-60) <sup>†</sup>	5 [2-10]	6 [2-11]	8 [4-14]	<0.001
Fear of falling (0-30) <sup>†</sup>	0 [0-2]	1 [0-3]	1 [0-5]	<0.001
Physical activity (0-2305) <sup>†</sup>	481 [267-720]	480 [286-731]	407 [228-638]	0.002
Physical performance (0-12) <sup>†</sup>	8 [6-9]	7 [5-9]	7 [3-9]	<0.001
Functional limitations (0-6) <sup>†</sup>	1 [0-2]	1 [0-2]	1 [0-3]	<0.001

BMI Body Mass Index; MMSE Mini-Mental State Examination.

<sup>#</sup> Presented as mean (Standard Deviation), differences tested using ANOVA

<sup>†</sup> Presented as median [interquartile range], differences tested using Kruskal-Wallis test

<sup>‡</sup> Presented as percentages, differences tested using the chi-squared test

**Table 2.** The associations between physical activity and time to first fall or time to recurrent falling

Model	HR	CI	p-value
Time to first fall			
physical activity	0.98	0.96-1.01	0.13
physical activity + confounders	0.98	0.96-1.00	0.11
Time to recurrent falling			
physical activity	0.93	0.90-0.97	<0.001
physical activity + confounders	0.96	0.92-0.99	0.02

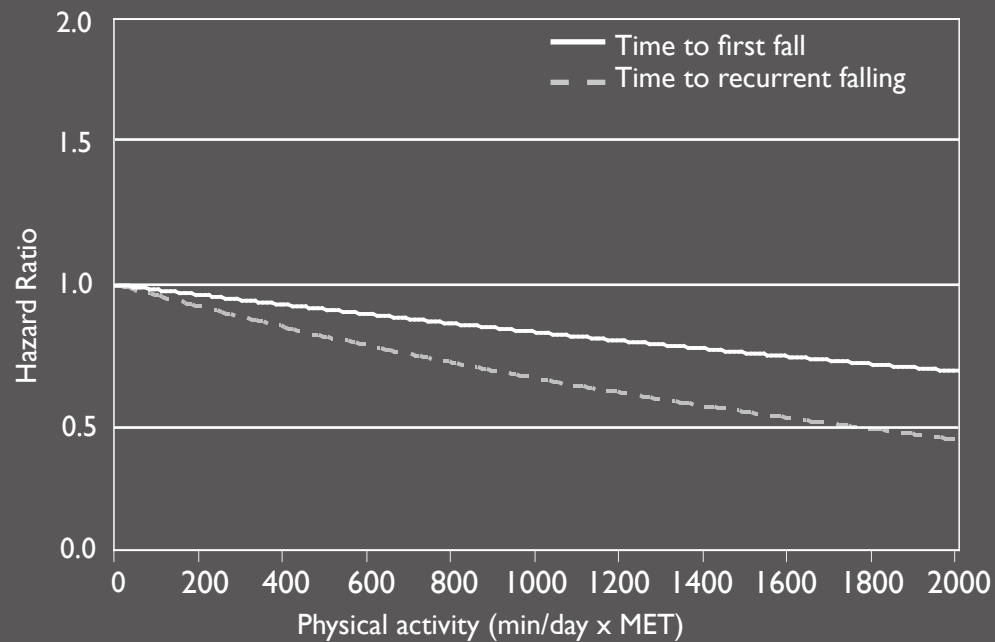
Hazard Ratios (HR) and 95 % Confidence Interval; (CI) are presented per 100 units (i.e. minutes per day × MET score) increase in physical activity . Confounders were age, sex, BMI, chronic diseases, psychotropic medication, MMSE, depressive symptoms and fear of falling

association between physical activity and time to recurrent falling. The interactions between physical activity and physical performance ( $p=0.72$ ) or functional limitations ( $p=0.59$ ) were not significant. Therefore, further analyses were not stratified for physical performance or functional limitations. A linear association between physical activity and time to recurrent falling was found: the hazard ratio (HR) for an increase in physical activity of 100 units was 0.93 (CI: 0.90-0.97) (Table 2). After adjustment for potential confounders, the association remained significant. After additional adjustment for physical performance or functional limitations, the association became not significant (HR=0.97, CI: 0.93-1.00 for both models). In Figure 1, we modeled the association between physical activity and time to recurrent falling. To give insight in the actual data, physical activity in categories of 400 units was plotted against the risk of recurrent falling in Figure 2. In contrast to the continuous analysis, no significant association between physical activity in categories and recurrent falling was found due to low numbers of participants, especially in the highest categories.

## Discussion

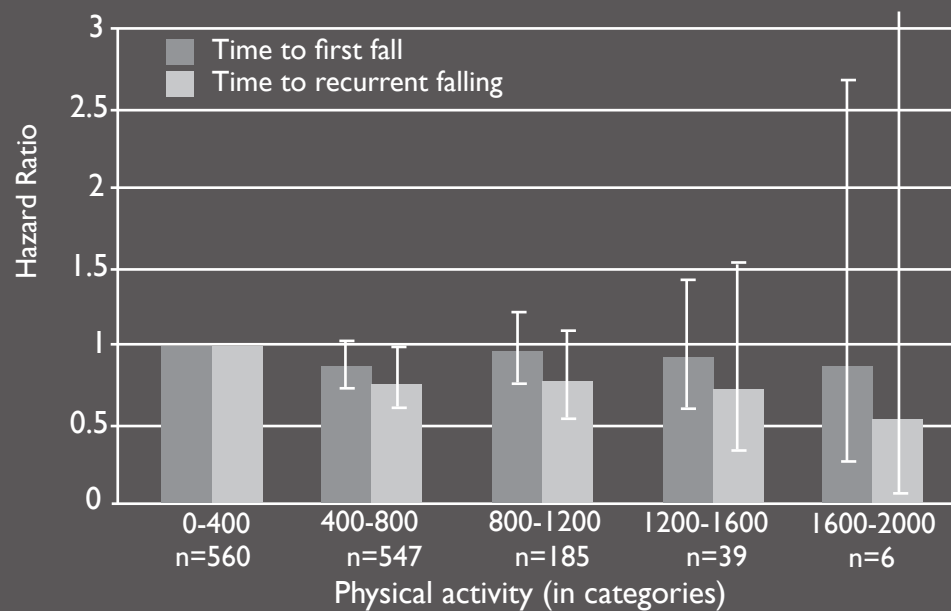
This is the first study that examined whether the relationship between physical activity and (recurrent) falling was U-shaped. Testing did not confirm a U-shaped association between physical activity and time to first fall or between physical activity and time to recurrent falling. No statistically significant association was found between physical activity and falling, while an increase in physical activity of 100 units led to a 4 % decrease in risk of recurrent falling. These associations were not modified by physical performance or functional limitations.

Some studies found that high levels of physical activity were associated with an increased fall risk,<sup>6,10</sup> whereas other studies found that low levels of physical activity were associated with an increased fall risk.<sup>9,11,12</sup> The combination of both low and high levels being associated with fall risk has led to the hypothesis that the relationship between physical activity and fall risk may be U-shaped. The results of the current study do not support this hypothesis, neither with respect



**Figure 1.** The adjusted associations between physical activity and time to first fall and time to recurrent falling

The Hazard Ratios are plotted against physical activity (min/day x MET) after adjustment for age, sex, BMI, chronic diseases, psychotropic medication, MMSE, depressive symptoms, and fear of falling. The solid line represents the time to first fall ( $HR = \exp(-0.000198 \times \text{physical activity})$ ), the dashed line represents the time to recurrent falling ( $HR = \exp(-0.000436 \times \text{physical activity})$ ).



**Figure 2.** The associations between physical activity (in categories) and time to first fall and time to recurrent falling

The Hazard Ratios for time to first fall and time to recurrent falling are plotted against physical activity in categories of 400 units after adjustment for age, sex, BMI, chronic diseases, psychotropic medication, MMSE, depressive symptoms, and fear of falling.

to falling nor with respect to recurrent falling. This is in line with other large cohort studies which reported either a gradual increase or decrease in risk ratios for higher physical activity categories.<sup>10,12</sup>

In the current study, physical activity was not significantly associated with fall risk. Three other cohort studies reported an increased fall risk in men<sup>10</sup> and a decreased fall risk in women<sup>12</sup> or in persons living in a residential care setting<sup>11</sup> in higher physical activity categories as compared with the lowest category. Perhaps lack of an association in our study is due to an interaction with sex. However, the interaction term for physical activity x sex was not significant ( $p=0.89$ ). A second explanation may be that in our study, participants with high levels of physical activity were underrepresented causing an underestimation of the actual relationship. However, our sample is representative for the community-dwelling older population in the Netherlands. Third, these three studies and the current study differed in population (men<sup>10</sup> vs. women<sup>12</sup> vs. residential care setting<sup>11</sup>), physical activity measures (validated questionnaires<sup>10</sup> vs. operational definitions<sup>12</sup>), and outcome measures (four month fall risk<sup>10</sup> vs. proportion fallers<sup>12</sup>). It is likely that the contrasting findings are explained by differences in population and methodology.

The association between physical activity and recurrent falling has been studied only once before. A study among persons of 70 years and older living in a residential care setting showed that the risk of recurrent falling decreased at higher levels of physical activity.<sup>11</sup> Our findings in community-dwelling older persons are in line with this study: an increase of 100 units led to a 4 % lower risk of recurrent falling.

It has been suggested that in this type of study adjustment should be made for baseline mobility.<sup>7</sup> Like physical performance and functional limitations, mobility is a measure of physical functioning. In the current study, physical functioning did not modify the relationship between physical activity and (recurrent) falling. However, physical functioning may not only act as an effect modifier or confounder, it may also be a mediator: physical activity and physical functioning could mutually affect each other and consequently the fall risk. In line with previous studies, we regarded physical performance and functional limitations as mediators and did not adjust for it in the final models.<sup>10,11</sup>

The current results suggest that older people should increase their level of daily physical activity. After adjustment for confounders, an increase in daily physical activity of 100 units is associated with a 4 % lower risk of recurrent falling. One hundred units equal 30 minutes per day of walking, 20 minutes of swimming or 40 minutes of billiards. Thus, if all older persons increase their physical activity level with 100 units, 4 % may be prevented to become recurrent fallers. In addition, given the beneficial effects of physical activity on other health outcomes, it is very

important to observe that, other than expected in the literature, highly active persons do not have an increased risk of falling.

Other than expected, no interactions were found with physical performance or functional limitations. Thus, these results do not confirm the expectation that highly active persons with poor physical functioning fall more often due to an incongruence of what they are safely able to do and what they actually do. Possibly, older persons with poor physical function adapt the level and performance of activities to their abilities. As described in the introduction, other studies found interactions with leg extension strength and use of a walking aid.<sup>10,11</sup> Leg extension strength and use of a walking aid are aspects of physical functioning, but do not measure the full concept. In addition, as described above, the different findings may be due to differences in study sample and the measurement of physical activity and falling.

A strength of this study is the content of physical activity measured. Many physical activity questionnaires only assess the frequency or duration of a limited number of physical activities<sup>7</sup> and do not include light household activities, although these are important in older persons.<sup>33</sup> In addition, if intensity of activities is not included, the time spent doing activities may give a false impression of a person's level of activity. For example, a person with poor physical performance may need more time to finish the same activity than a person with adequate physical performance. We corrected for this phenomenon by weighing for the intensity of an activity. A limitation of this study is that physical activity was based on self-reports. However, this questionnaire has been validated for older persons.<sup>25</sup> Second, we excluded five participants with extremely high scores for physical activity (i.e. >2000 min/day x MET). If the analyses are repeated including these five participants, a U-shaped association is observed between physical activity and time to first fall ( $p$  for physical activity<sup>2</sup>=0.07). However, the number of participants in our study with such extremely high activity patterns is too small and more research in this specific group is necessary before final conclusions can be drawn. Third, non-response analysis showed that those who were excluded from the analyses were less active and more often recurrent fallers. Thus, the relationship may be an underestimation of the actual relationship.

In conclusion, the hypothesized U-shaped relationship between physical activity and falling could not be confirmed. At higher levels of physical activity, the risk of recurrent falling decreased, while no association was found with fall risk in general. Moreover, the associations did not seem to be modified by level of physical functioning.

## Acknowledgements

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# 6

## **Prevention of fall incidents in patients with a high risk of falling: design of a randomised controlled trial with an economic evaluation of the effect of multidisciplinary transmural care**

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Deelnemer (95 jaar): “Van mijn kinderen mag ik eigenlijk niet mee doen aan het onderzoek, ze vinden me te oud. Maar ik doe het stiekem toch!”

## Abstract

**Objective** Annually, about 30 % of the persons of 65 years and older falls at least once and 15 % falls at least twice. Falls often result in serious injuries, such as fractures. Therefore, the prevention of accidental falls is necessary. The aim is to describe the design of a study that evaluates the efficacy and cost-effectiveness of a multidisciplinary assessment and treatment of multiple fall risk factors in independently living older persons with a high risk of falling.

**Methods** The study is designed as a randomised controlled trial (RCT) with an economic evaluation. Independently living persons of 65 years and older who recently experienced a fall are interviewed in their homes and screened for risk of recurrent falling using a validated fall risk profile. Persons at low risk of recurrent falling are excluded from the RCT. Persons who have a high risk of recurrent falling are blindly randomised into an intervention (n=100) or usual care (n=100) group. The intervention consists of a multidisciplinary assessment and treatment of multifactorial fall risk factors. The transmurial multidisciplinary approach entails close cooperation between geriatrician, primary care physician, physical therapist, and occupational therapist and can be extended with other specialists if relevant. A fall calendar is used to record falls during one year of follow-up. Primary outcomes are time to first and second falls. Three, six and twelve months after the home visit, questionnaires for economic evaluation are completed. After one year, during a second home visit, the secondary outcome measures are reassessed and the adherence to the interventions is evaluated. Data will be analysed according to the intention-to-treat principle and also an on-treatment analysis will be performed.

**Discussion** Strengths of this study are the selection of persons at high risk of recurrent falling followed by a multidisciplinary intervention, its transmurial character, and the evaluation of adherence. If proven effective, implementation of our multidisciplinary assessment followed by treatment of fall risk factors will reduce the incidence of falls.

Trial registration: Current Controlled Trials ISRCTN11546541.

## Background

Fall incidents are the third cause of chronic disablement in older persons according to the WHO.<sup>1</sup> Annually, about 30 % of persons older than 65 years falls at least once and 15 % falls at least twice.<sup>2-4</sup> The consequences of falling are severe: 5 % of the falls leads to a fracture and 5 % of the falls leads to other serious injuries.<sup>5,6</sup> About one in four fallers consults a hospital emergency room or primary care physician after the fall.<sup>6</sup> These facts emphasize the necessity of measures to prevent falling in older persons.

The pathogenesis of falling is multifactorial.<sup>2,7</sup> Causes of falling are impairments in balance, gait, muscle strength, visual acuity, cognition, chronic diseases, and use of psychotropic medications.<sup>8-12</sup> Many studies have investigated risk factors of falling<sup>2,13-15</sup> and several risk profiles have been developed,<sup>4,14,16-18</sup> which can be used to identify older persons at high risk of falling.

Interventions to reduce the risk of falling have been successful to a varying degree. Home visits by nurses were found to be ineffective,<sup>19</sup> whereas Tai Chi, exercise therapy and multifactorial interventions led to a decrease in falls.<sup>20-22</sup> A meta-analysis showed that a multifactorial fall risk assessment and management program was effective in all older populations investigated, both with a high or low risk of falling.<sup>23</sup> A systematic Cochrane review of preventive interventions showed a positive effect in older persons with a history of falling or in those who were known to have risk factors.<sup>24</sup>

The guideline “Prevention of fall incidents in older persons”, developed by the Dutch Institute for Healthcare Improvement (CBO), recommends a systematic assessment of fall risk factors in independently living older persons with a high risk of falling. Based on this assessment, a specific and individual treatment plan has been designed.<sup>25</sup> A similar strategy has previously been investigated in the Prevention Of Falls in the Elderly Trial (PROFET) study in the UK, leading to a fall incidence reduction of 50 %.<sup>13</sup> However, other studies that evaluated the effectiveness of multifactorial fall prevention strategies were not effective.<sup>26-31</sup> Only one trial studied the cost-effectiveness of a multifactorial intervention program in the USA and reported that the intervention was associated with fewer falls and lower costs.<sup>32</sup> Although many geriatric outpatient clinics have recently started “multidisciplinary fall prevention services”, no studies have yet been conducted assessing the effectiveness and cost-effectiveness of such a multifactorial intervention program in older persons with a high risk of recurrent falling.

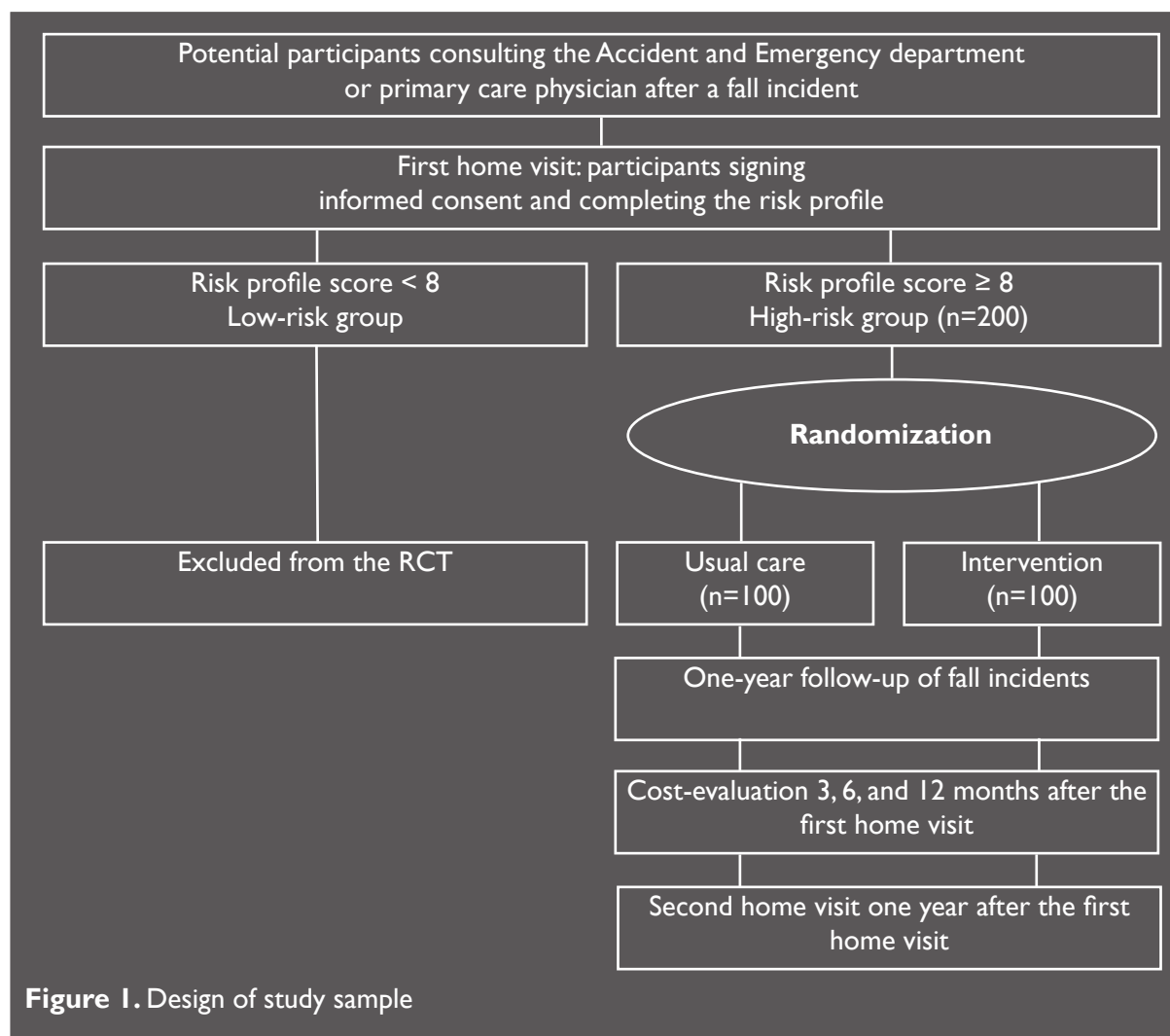
The objective of this article is to describe the design of a randomised controlled trial that aims to reduce the fall risk in older persons with a high risk of falling. The intervention consists of a systematic assessment of the putative causes of falling and subsequent targeted individualised preventive measures. Unique characteristics of this trial are the evaluation of fall risk factors and

subsequent treatment of persons with a high risk of recurrent falling, and the close collaboration between the hospital and primary care physician (transmural care). Both the effectiveness and cost-effectiveness of the intervention will be assessed.

## Method

### *Study design and randomisation*

This study is a randomised controlled trial (RCT) with a one-year prospective follow-up. Simultaneously, an economic evaluation will be conducted. The Medical Ethics Committee of the VU University Medical Center has approved the study design, protocols, and informed consent procedures. Figure 1 shows the design of the study. Potential participants are contacted and after signing informed consent a validated fall risk profile<sup>16</sup> is used to select participants with a high risk of recurrent falling (score of 8 and higher). Participants with a low-risk of recurrent falling are excluded from the RCT. Participants living in a residential home are right away assigned to the high-risk group, which is in accordance with the recommendations of the Dutch Institute for Healthcare Improvement (CBO) guideline.<sup>25</sup> Participants in the high-risk group are blindly



randomised into two groups: the intervention group and the usual care group. Prior to the onset of the trial a randomization schedule is made by a statistician. A block randomization of 4 per block is used. Using the sequence of this schedule, opaque envelopes are numbered and filled with group names. When a participant is designated to the high-risk group, the interviewer, who is unaware of the content, opens the envelope with the lowest number.

### *Study population*

The study population consists of persons of 65 years and over, who consult the Emergency Department (ED) of the VU University Medical Center (Amsterdam, the Netherlands) or their primary care physician between April 2005 and April 2007 after a fall incident. Inclusion criteria are living independently or in a residential home, living in the vicinity of the VU University Medical Center, and having experienced a fall. Exclusion criteria are inability to sign informed consent, inability to provide a fall history, fall due to a traffic or occupational accident, living in a nursing home, and acute pathology requiring long-term rehabilitation, such as a stroke.

Two hundred high-risk participants will be included in the intervention study, of which we will enrol 100 participants in the intervention group and 100 in the control group. With a significance level of 0.05, a power of 80 % and an expected difference in fall incidence of 50 %<sup>13</sup> between the intervention and control group, 57 participants are needed both in the intervention and in the control group. Taking into account a drop-out rate of 30 %, a minimum of 82 participants are needed in each group. With 100 persons in both the intervention and control group, the numbers are certainly high enough to detect statistical significant differences.

### *Procedure*

All persons who consult the ED or primary care physician after a fall receive usual care. Within two weeks after the initial presentation, written information is sent and several days thereafter, the potential participants are contacted by telephone. All actual participants (who sign informed consent) are visited at their homes by a trained interviewer within 3 months after the fall incident. During the first home visit, the fall risk profile,<sup>16</sup> fall history, independence in activities of daily living, quality of life, and physical performance are measured. All high-risk participants will report falls during at least one year using a fall calendar and receive a cost-evaluation questionnaire at 3, 6, and 12 months after the first home visit. The times to first and second fall are the primary outcome measures. One year after the first home visit, they are visited a second time to reassess the activities of daily living, quality of life, and physical performance. Scores on these questionnaires and tests are used as secondary outcome measures. Furthermore, the treatment adherence and medication use are evaluated. Table 1 presents an overview of the procedure and measurements. The measurements used are described later on in this article.

**Table 1.** Overview of procedure and measurements

	Months	Measurements	Purpose
1st home visit	0	fall risk profile	selection high risk participants
		fall history	assessment of fall risk factors, confounders
		activities of daily living	secondary outcome measure
		quality of life	secondary outcome measure
		medication use	assessment of fall risk factors
		medical history	assessment of fall risk factors, confounders
		physical performance	secondary outcome measure
1st follow-up	3	1st calendar sheet	primary outcome measure
		3 months cost-evaluation	primary outcome measure
2nd follow-up	6	2nd calendar sheet	primary outcome measure
		6 months cost-evaluation	primary outcome measure
3rd follow-up	9	3rd calendar sheet	primary outcome measure
2nd home visit	12	activities of daily living	secondary outcome measure
		quality of life	secondary outcome measure
		medication use	treatment adherence
		medical history	secondary outcome measure, confounders
		physical performance	secondary outcome measure
		treatment adherence	confounder, interpretation of the results
4th follow-up	12	4th calendar sheet	primary outcome measure
		12 months cost-evaluation	primary outcome measure

*Intervention*

An extended multidisciplinary assessment starts with a visit to the geriatric outpatient clinic. A multifactorial fall risk assessment will be conducted aiming to identify modifiable fall risk factors. The assessment of fall risk factors and design of the treatment plan is based on the directives in the CBO guideline “Prevention of fall incidents in older persons”.<sup>25</sup> The assessment consists of a general medical and drug history, a fall and mobility history and physical examination. According to the recommendations of the CBO guideline special emphasis is placed on signs and symptoms of potentially modifiable fall and fracture risk factors such as postural hypotension, visual impairment, parkinsonism, osteoporosis, osteoarthritis, gait disorders, psychotropic and cardiac drug use, and environmental hazards. When indicated, additional diagnostic tests can be performed (e.g. laboratory tests or imaging). Based on the assessment of risk factors an individually tailored treatment regimen aimed at reduction of the fall risk is composed in close collaboration with the primary care physician of the participant. In the Netherlands, the primary care physician has a central role in the coordination of specialist’s care, home care and physiotherapy among others. The collaboration facilitates the transmural continuity of care that has been lacking in most previously performed fall risk reduction trials. The multifactorial treatment can consist of, for example, withdrawal of psychotropic drugs, balance and strength

exercises by a physical therapist, home hazard reduction by an occupational therapist, or referral to an ophthalmologist or cardiologist. Per participant and per diagnosis the International Classification of Diseases code (ICD10) and recommendations are reported to document the treatment regimen.

### *Usual Care*

Usual care in the Netherlands after a fall mainly consists of treatment of the consequences of the fall. Although the CBO guideline was released in 2004,<sup>25</sup> multifactorial fall risk prevention has not yet been implemented by primary care physicians or at the ED. In primary care settings 'usual care' only incidentally includes systematic assessment and treatment of fall risk factors.

### *Measurements*

#### *Baseline assessment*

During the first home visit, the risk of recurrent falling, fall history, medical history, medication use, independence in activities of daily living, and quality of life are assessed. Risk of falling is assessed using a fall risk profile.<sup>16</sup> This profile, which was developed and validated in the Longitudinal Aging Study Amsterdam,<sup>16</sup> is used to screen participants with a high risk of recurrent falling. Recurrent falling is defined as 2 or more falls in a 6-month period.<sup>8,16,18</sup> This profile consists of 7 questions, 2 measurements (handgrip strength and body weight), and 2 interaction items. To measure handgrip strength a digital strain-gauged dynamometer (Takei TKK 5401, Takei Scientific Instruments Co. Ltd., Tokyo, Japan) is used. To measure body weight, a calibrated balance beam scale is used. On each item, points are scored and the scores are summed (range 0-30). Table 2 presents the diagnostic values of the risk profile for different cut-off points on the fall risk score for 426 participants in the LASA-study who reported at least one fall in the previous year.<sup>16</sup> For this study, participants are defined at high risk of recurrent falling as the total score is 8 or higher. For an optimal combination of sensitivity and specificity, a cut-off score of 11 should be used. However, with a cut-off score of 11, a low sensitivity is obtained and too many participants with a high risk of recurrent falling will be missed. To ensure that not too many low risk participants are falsely diagnosed as high risk, the specificity should not be too low. At a cut-off score of 8, the sensitivity and specificity are higher than 50 and 70 %, respectively.

Fall history is assessed with the fall history instrument (Carefall Triage Instrument, version 007), which is a questionnaire developed by the Academic Medical Center, the VU University Medical Center, and the Erasmus Medical Center, the Netherlands. The fall history collects data on the circumstances of the last and previous falls, mobility and risk factors of bone loss and osteoporosis, social status, and general health. Medical history is assessed using a questionnaire on self-reported (chronic) diseases both in the past and present. The questionnaire includes 7

**Table 2.** Diagnostic values of the risk profile at different cut-off points in the total risk score

Cut-off in de total risk score	% at high risk group	Sensitivity (%)	Specificity (%)	$\Sigma$ (%)	PV+ (%)	PV- (%)	P <sub>falls</sub>
0 vs $\geq 1$	78.2	95.1	11.7	106.8	41.1	78.8	0.10 vs 0.34
0-1 vs $\geq 2$	69.7	86.1	22.1	108.2	41.8	71.0	0.11 vs 0.36
0-2 vs $\geq 3$	61.5	79.9	33.8	113.7	43.9	72.1	0.13 vs 0.39
0-3 vs $\geq 4$	51.4	70.8	47.3	118.1	46.6	71.4	0.14 vs 0.43
0-4 vs $\geq 5$	46.0	66.0	54.5	120.5	48.5	71.2	0.15 vs 0.46
0-5 vs $\geq 6$	39.2	60.4	64.0	124.4	52.1	71.4	0.17 vs 0.50
0-6 vs $\geq 7$	35.4	55.6	68.0	123.6	53.0	70.2	0.17 vs 0.52
0-7 vs $\geq 8$	32.6	52.1	71.2	123.3	54.0	69.6	0.18 vs 0.54
0-8 vs $\geq 9$	29.8	48.6	74.3	122.9	55.1	69.0	0.19 vs 0.56
0-9 vs $\geq 10$	27.9	46.5	76.6	123.1	56.3	68.8	0.20 vs 0.57
0-10 vs $\geq 11$	21.4	41.0	85.6	126.6 <sup>#</sup>	64.8	69.1	0.22 vs 0.91
0-15 vs $\geq 16$	5.9	13.9	97.7	111.6	80.0	63.6	0.28 vs 0.77

$\Sigma$  sum of sensitivity and specificity; <sup>#</sup> maximum sum; PV+ positive predictive value; PV- negative predictive value; P<sub>falls</sub> probability of recurrent falls in low risk versus high risk group

The sample used in LASA to develop the fall risk profile included relatively healthy community dwelling older persons of which a large part reported zero previous falls.<sup>16</sup> In contrast, all participants of this study have a history of at least one recent fall and also include people living in a home for the elderly. Thus, the participants in our study are expected to have poorer mobility and more functional limitations and, on average, to score higher on the risk profile. The diagnostic values presented here are the recalculated values using the data of 426 independently living participants of the LASA study who fell at least once.<sup>16</sup>

major chronic diseases, i.e. chronic lung diseases, cardiac diseases, vascular diseases, stroke, diabetes mellitus, malignant neoplasms, and joint disorders (i.e. osteoarthritis and rheumatoid arthritis). In addition, participants are asked to indicate any other chronic disease, including psychological diseases, which they have or have had. Medication use is assessed by directly copying the names of drugs used in the previous two weeks from the containers. The name, doses per unit, number of times taken per day, time of administration, doses per intake, purpose, prescription or over the counter (OTC) and whether the drug has been prescribed after the fall are assessed for each drug. This information is compared to medication records of the public pharmacy. Level of independence in activities of daily living (ADL) will be examined using the Barthel Index (range 0, fully dependent, to 20, fully independent).<sup>33</sup> The level of functioning on more complex daily activities will be examined using a scale of instrumental ADL introduced by Lawton and Brody (range 0, fully dependent, to 8, fully independent).<sup>34</sup> Quality of Life (QoL) is examined using the Dutch translations of the SF-12 and the EQ-5D. The SF-12 consists of 12 items and is an abbreviated version of the SF-36.<sup>35</sup> The SF-12 has been designed and validated to measure health related QoL in large population studies.<sup>35,36</sup> The EQ-5D (EuroQol) has been developed to generate a general index of experienced health and for the assessment of Quality Adjusted Life Years (QALY). It is therefore suitable for economic evaluations.<sup>37</sup> The assessment



consists of 5 items (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and a visual analogue scale (0, worst, to 100, best imaginable health state).<sup>37</sup> The fall history, ADL, and QoL questionnaires are sent to the participants prior to the first home visit. Participants are asked to complete these questionnaires before the home visit. The visiting researcher assists participants who are unable to complete these questionnaires independently.

To assess physical performance, four tests are conducted (see Figure 2). The chair stands test is a standardized test in which the participant stands up and sits down for five consecutive times as fast as possible with the arms folded in front of the chest.<sup>38</sup> During the walk test the participant walks 3 meter along a line, turns 180 degrees and walks 3 meters back along the line.<sup>38</sup> Time is recorded in both tests from start to finish. The functional reach is a standardized test to measure the ability to maintain balance while reaching forward.<sup>39</sup> The participant stands parallel to a wall with one arm horizontally stretched and then leans forward while keeping the arm stretched and horizontal. The distance between the start and end position of the index finger is measured in centimetres. The modified Romberg test is used as a measure for standing balance. The participant stands consecutively with the feet apart at shoulder width, with the feet side to side, with one foot in front of the other but not in one line, and with the feet in one line and heel against toe (tandem stand). All positions are performed first with the eyes open and then with the eyes closed. The participant scores 1 point per position continued for at least 10 seconds (range 0, poor balance, to 4, good balance).<sup>40</sup>

#### *Follow-up*

At the first home visit, the participants receive a fall calendar.<sup>16</sup> For the period of one year, the participants tick per week whether they did or did not fall during that week. A fall is defined as an unintentional change in position resulting in coming to rest at a lower level or on the ground.<sup>41</sup> Once per 3 months the participants return a calendar sheet by mail. When no sheet is received, or when the sheet is completed incorrectly, we inquire by telephone whether, and if yes, when the participant has fallen in the past 3 months.

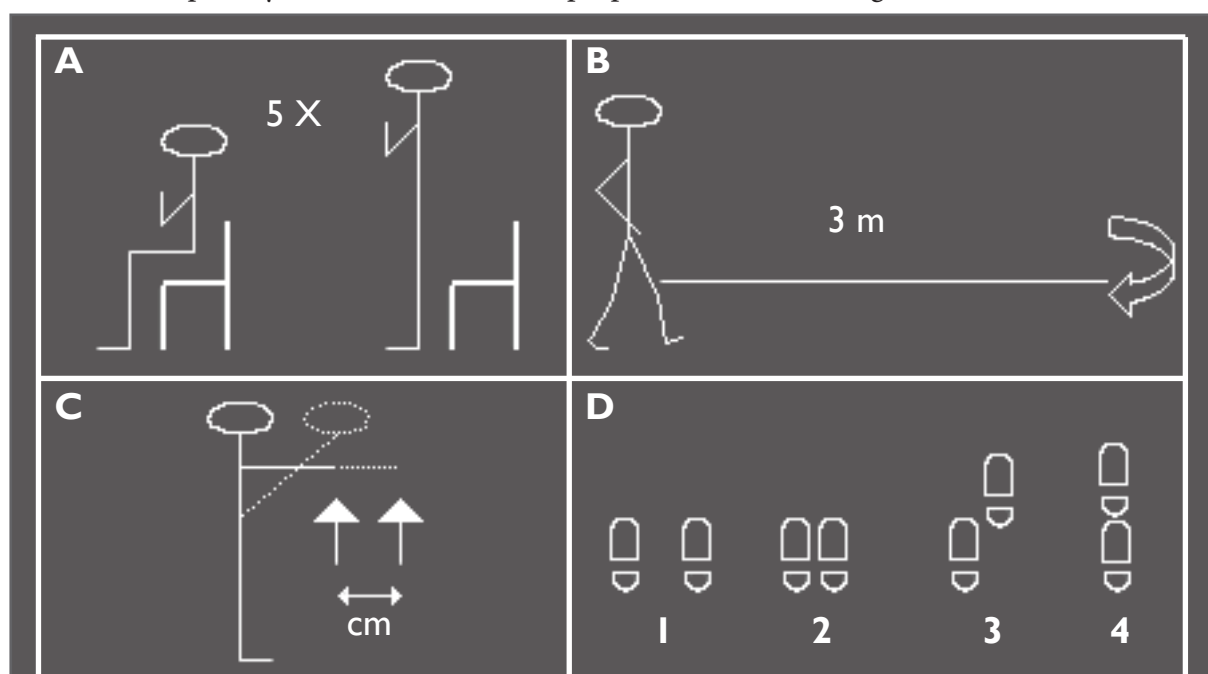
The cost-evaluation questionnaire registers the costs made to prevent a new fall or the consequences of a new fall. The questionnaire assesses: the number of visits to physicians, therapists or day care centres; amount and aim of surgical procedures; number of days of admission to a hospital, home or nursing home; purchase of aids and adaptations in the home environment. The questionnaires are conducted 3, 6, and 12 months after the first home visit. The 3 and 6 months questionnaires are sent by mail and apply to the preceding 3 months. The 12 months questionnaire is assessed during the interview of the second home visit. This questionnaire applies to the preceding 6 months. When no questionnaire is received, or when it is completed incorrectly, the questionnaire will be completed by telephone.

During the second home visit, one year after the first visit, the same physical performance tests are conducted along with a reassessment of fall related healthcare costs, medical history, medication use, quality of life, and activities of daily living. In addition, in the intervention group, adherence to the treatment regimen is evaluated. Treatment adherence in the intervention group is evaluated per recommendation given. Recommendations regarding changes in medication are evaluated by reassessing the medication use as described above. Adherence to all other recommendations (such as referrals to physical therapy or cardiologist) is assessed by asking whether, to what extent, and how the recommendations of the intervention were effected. The information from the participant is completed with information from the rapports of the involved specialists.

### Statistics

Data will be primarily analysed according to the intention-to-treat principle, i.e. including all randomised participants, regardless of whether they received or did not receive the intervention. Subsequently, the results of the intention-to-treat analysis will be compared to the results of an on-treatment analysis.

At baseline, differences in baseline characteristics will be compared between the intervention and control group to examine comparability between the two groups. To examine the effectiveness of the multidisciplinary transmural care, Cox proportional hazards regression will be conducted,



**Figure 2.** Physical performance tests

A Chair stands test

B Walk test

C Functional reach

D Modified Romberg test

with time to first fall and time to second fall within one year of follow-up as outcome measures, and with age, gender, and living situation as covariables. Subsequently, multiple linear regression analyses will be used to compare differences in secondary outcome measures (ADL-score, QoL, physical performance and morbidity data) at 12 months follow-up between intervention and control group.

The economic evaluation will be conducted from a societal perspective, which implies that all costs and outcomes are taken into account. The economic evaluation will involve calculating cost-effectiveness and cost-utility ratios. The incremental costs and effects of the intervention will be compared with usual care. The difference in costs of the intervention group and usual care group will be computed using bootstrapping techniques. Uncertainty ratios will be presented on cost effectiveness and cost utility planes. Acceptability curves will also be estimated. These present the probability that the intervention is cost-effective given a ceiling ratio that policy makers are willing to invest.

#### *Progress of the study*

In April 2005 the inclusion of the participants started and will continue until July 2007. The follow-up will end in July 2008 and then data-analysis will be initiated.

### **Discussion**

The strengths of this study, are the screening of participants at high risk of falling, its transmural design and evaluation of treatment adherence. In previous studies,<sup>13,42</sup> as in our study, participants were selected at EDs or primary care centers. These participants are a mix of once-fallers and recurrent fallers. In previous studies, the participants assigned to the intervention group were not selected for risk of falling. We expect that participants at high risk of recurrent falling will benefit most from the intervention and, therefore, we expect to find an enhanced (cost-) effectiveness of the preventive measures.

Furthermore, in previous studies, the recommendations of the intervention were drawn up by the geriatrician and executed by the primary care physician,<sup>13,42</sup> whereas in this study, the primary care physician is actively involved in the process of drawing up the recommendations, and the intervention is initiated by the geriatrician and followed up by both the geriatrician and primary care physician. We therefore expect to have a better coordination of the transmural care.

In several fall prevention studies, active participation has been associated with better outcomes<sup>43,44</sup> and poor treatment adherence has been reported as a possible explanation for lack of effect of the intervention.<sup>45</sup> In contrast to previous studies,<sup>13,42,43</sup> we not only score the

number of recommendations that are effected, but also add an evaluation of how the treatment recommendations are effected. This information will add to the interpretation of the results.<sup>44</sup>

The results of this trial will provide clinicians in the field of aging with more knowledge on treatment of older persons at high-risk of recurrent falling. If proven cost-effective, a multidisciplinary assessment and treatment of fall risk factors in persons with a high risk of recurrent falling will lower the risk of falling and consequently lead to reduced incidence and costs of falls.

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# 7

## **Validation of the LASA fall risk profile for recurrent falling in older recent fallers**

Submitted as: GMEE Peeters, SMF Pluijm, NM van Schoor, PJM Elders, LM Bouter, P Lips.  
Validation of the LASA fall risk profile for recurrent falling in older recent fallers



Interviewer: “Bent u in de afgelopen 3 maanden gevallen, gestruikeld of uitgegleden?”

Deelnemer 1: “Ja, maar dat telt niet mee, want het was mijn eigen schuld.”

Interviewer: “Bent u in de afgelopen 3 maanden gevallen, gestruikeld of uitgegleden?”

Deelnemer 2: “Ja, maar dat telt niet mee, want ik kon er niks aan doen.”

**Abstract**

**Objective** The fall risk profile developed in the Longitudinal Aging Study Amsterdam (LASA) identifies community-dwelling elderly at high risk for recurrent falling. This study assessed the predictive validity of this profile in older persons who consulted the Emergency Department (ED) or family physician after a fall.

**Methods** Persons of 65 years and older who consulted the ED or family physician after a fall (n=408). The risk of recurrent falling was assessed using the LASA fall risk profile. Falls were prospectively reported with a calendar during one year. Recurrent falling was defined as  $\geq 2$  falls within a period of 6 months.

**Results** During one year of follow-up, 76 (18.6 %) participants became recurrent fallers. The Area Under the receiver-operator Curve (AUC) was 0.65 (95 % Confidence Interval: 0.58-0.72). At a cut-off value of 8, the sensitivity was 56.6 % (CI: 51.8-61.4), the specificity was 71.4 % (CI: 67.0-75.8), the positive predictive value was 34.1 % (CI: 29.5-38.7), and the negative predictive value was 85.6 % (CI: 82.2-89.0).

**Conclusion** The discriminative ability of the LASA fall risk profile was moderate. The predictive validity of the LASA fall risk profile to identify recurrent fallers is limited among older persons who consulted the Emergency Department or family physician after a fall.

## Introduction

Falling is a major health problem in old age. About 30 % of the community-dwelling persons of 65 year and older falls once a year and 15 % falls at least twice a year.<sup>1-3</sup> The consequences of falling are severe: 5 % of all falls lead to a fracture and 5 % lead to other serious injuries.<sup>4</sup> About 20 to 25 % of all fallers and 50 % of all injurious fallers consult an Emergency Department (ED) or family physician after the fall.<sup>4-6</sup>

Because of the increasing number of older persons in the next decades, the number of older persons with falls is expected to rise as well. Even with maximum expansion of primary care and geriatric health care resources, treatment of every older person to prevent further falls is not feasible. It may be more (cost-)effective to limit the intervention to those older persons with the highest fall risk.<sup>7</sup> To identify persons with the highest fall risk a risk profile can be used.

Several risk profiles for identifying community-dwelling older persons at high risk of falling have been developed.<sup>8-13</sup> It is known that the accuracy of prediction models differs in populations with different characteristics. Therefore, validation of risk profiles in other populations is necessary to assess the generalizability.<sup>14</sup> To our knowledge, only one of these risk profiles, the FROP-com, has been validated in populations who presented themselves after a fall.<sup>13</sup> However, the FROP-com predicts the risk of falling rather than the risk of recurrent falling. In the literature a distinction is made between once-fallers and recurrent fallers.<sup>15,16</sup> A single fall may be coincidental and may be caused mainly by environmental factors, whereas recurrent falls usually are caused by physical, cognitive and behavioural factors within the person.<sup>17</sup> Since the consequences of falling seem to be more severe in recurrent fallers than in once-fallers,<sup>18</sup> we were interested in the predictive validity of risk profiles for recurrent falling.

The fall risk profile developed in the Longitudinal Aging Study Amsterdam (LASA) predicts the risk of recurrent falling in older persons.<sup>10</sup> This profile consists of nine items including fall history, dizziness, functional limitations, grip strength, body weight, having a dog or cat in the household, fear of falling, alcohol intake, and level of education. Strengths of this profile are that it is easy to administer and that it has been developed in a large sample representative for the Dutch community-dwelling older population. The current study aimed to assess the predictive validity of the LASA fall risk profile in a clinically relevant population of older persons who consulted the ED or family physician after a fall. The discriminative ability of the fall risk profile was calculated to test the validity. The sensitivity, specificity, and positive and negative predictive values were calculated to explore the optimal cut-off value for triage in primary care settings.

In the LASA fall risk profile, the item “fear of falling” was measured using the Falls Efficacy Scale (FES).<sup>19,20</sup> This item consists of 10 sub questions, and is therefore not so practical for use

in daily practice. In the current study, fear of falling was also measured using the question “Are you afraid to fall”. The risk profile may be simplified by replacing the FES by this question. The second aim of this study was to examine whether this adaptation altered the predictive validity of the risk profile.

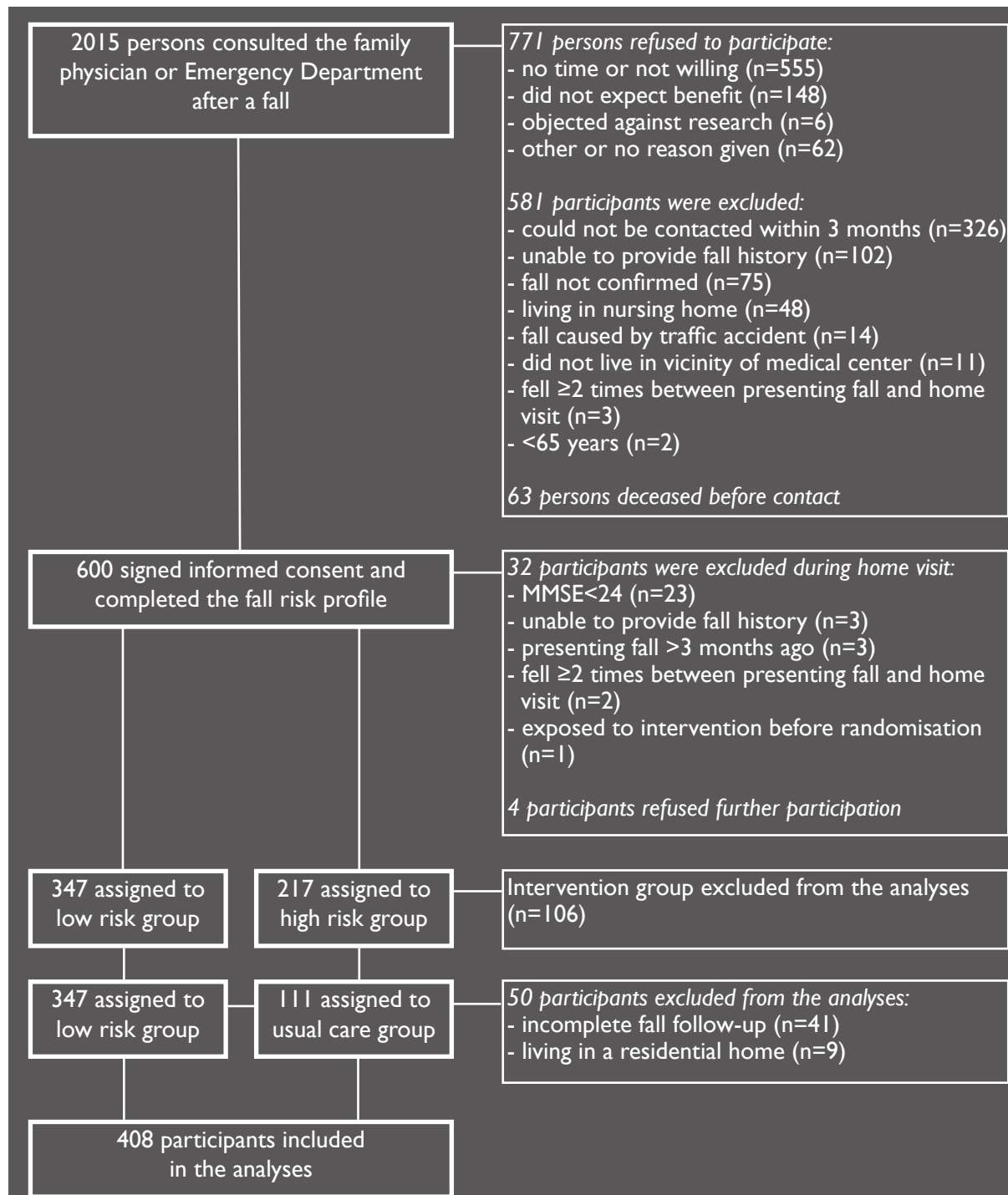
## Methods

### *Study population*

Data were used from the randomised controlled trial (RCT) ‘Prevention of fall incidents in older persons with a high risk of falling’ (Current Controlled Trials ISRCTN11546541). The design of this fall prevention trial (FPT) is described in detail elsewhere<sup>21</sup> and approved by the Medical Ethics Committee of the VU University Medical Center (VUmc), Amsterdam. In short, persons who reported themselves after a fall at the ED of the VUmc or their family physician between April 2005 and June 2007 were potential participants. Inclusion criteria were being 65 years or older, living independently or in a residential home in the vicinity of the VUmc and having had a recent fall. Exclusion criteria were inability to sign informed consent, inability to provide a fall history or scoring less than 24 points on the Mini-Mental State Examination (MMSE, assessed during the home visit explained below), presenting fall due to a traffic or occupational accident, living in a nursing home, and acute pathology requiring long-term rehabilitation such as a stroke. Participants who signed informed consent were visited at home by trained interviewers within 3 months after the presenting fall. During the home visit, the LASA fall risk profile (Appendix) was assessed. The RCT was done among persons at high risk of recurrent falling. For the purpose of this RCT, high-risk was defined as scoring 8 points or more on the LASA fall risk profile. Of the 2015 persons who presented themselves after a fall at the ED or family physician, 600 signed informed consent and completed the fall risk profile (Figure 1). After signing informed consent, 36 participants were excluded or refused further participation. Participants who scored 8 points or more on the risk profile (n=217) were randomised into an intervention (n=106) or usual care group (n=111). For the current study, data was used from the participants who scored less than 8 points (n=347) or who were assigned to the usual care group (n=111). Subsequently, participants living in a residential home were excluded from the analyses (n=9), because the risk profile was developed for the community-dwelling population. In addition, participants with incomplete fall follow-up were excluded from the analyses (n=41). Finally, data of 408 participants with complete fall follow-up was used in the current study.

### *Fall risk profile*

As described in the introduction, the fall risk profile was developed in LASA to predict the risk of recurrent falling in older persons.<sup>10</sup> The Longitudinal Aging Study Amsterdam is an ongoing interdisciplinary cohort study on predictors and consequences of changes in autonomy and well-being in older persons in the Netherlands.<sup>22</sup> The sample was stratified by age, sex, and five-years



**Figure 1.** Flow chart of the current study in the framework of the Fall Prevention Trial

mortality rate and is representative for the community-dwelling Dutch older population. A subsample of 1365 participants who were 65 years and older (as of January 1, 1996) reported falls during three years (from 1995/96 to 1998/99).<sup>10</sup> Backward logistic regression analyses identified nine items that predicted recurrent falling:  $\geq 2$  falls in preceding year, regular dizziness,  $>2$  functional limitations, poor grip strength, low body weight, having a dog or cat in the household, fear of falling,  $>15$  glasses of alcohol, and  $\geq 11$  years of education. Also, two interaction items

were included (i.e.  $\geq 2$  falls in preceding year  $\times$  fear of falling and  $>15$  glasses of alcohol  $\times$   $\geq 11$  years of education). Interaction items were combinations of items that increased the probability of becoming a recurrent faller more than the sum of the separate items. A weighted score based on the multivariate odds ratio was assigned to each of the items and the scores were summed to a total risk score (range 0-30). For example, an 80 year old lady who fell twice in the preceding year (4 points), who is afraid to fall again (2 points), and who owns a cat (2 points), would score 4 additional points for the combination of 2 falls in the preceding year and fear of falling. In total, she would score 10 points on the LASA fall risk profile. Higher scores indicate a higher risk of recurrent falling. The fall risk profile is included in the Appendix.

All items were measured in the same way in FPT as in LASA. Only the item 'functional limitations' was adapted in FPT. In LASA, this item was measured by asking the level of difficulty the participant had with using his/her own or public transportation, going up 15 steps without standing still, and cutting his/her own toenails. The answer categories were: 1) no, I cannot; 2) only with help; 3) yes, with much difficulty; 4) yes, with some difficulty; 5) yes, without help. If the participant had at least some difficulties (categories 1-4) with all three activities, three points were scored on this item. In FPT, this item was simplified by asking whether the participant did these activities independently (yes/no). If the participant answered no on all three activities, three points were scored on this item. Handgrip strength (item 4) was measured using a digital strain-gauged dynamometer (Takei TTK 5401, Takei Scientific Instruments Co. Ltd., Tokyo, Japan). Participants were instructed to put their arms along their body while maximally squeezing the handle with one hand during two seconds. The procedure was repeated twice per hand and the maximum scores of each hand were summed. Body weight (item 5) was measured using a calibrated balance beam scale. Fear of falling (item 7) was measured with the Falls Efficacy Scale (FES) which consists of 10 sub questions.<sup>19,20</sup> Participants scored how concerned they were to fall during 10 activities (0=not concerned at all, to 3=very concerned; range 0-30).

#### *Fear of falling*

In FPT, fear of falling was also assessed by asking the question "Are you afraid to fall?". Participants scored how afraid they were on a 10-point scale (1=not afraid at all; 10=very afraid to fall). If the participants scored 6 points or more (75th percentile), 2 points were assigned on this item.

#### *Recurrent falling*

At the home visit, the participants received a fall calendar.<sup>10</sup> For the period of one year, the participants ticked per week whether they did or did not fall during that week. A fall was defined as an unintentional change in position resulting in coming to rest at a lower level or on the ground.<sup>23</sup> Once per 3 months the participants returned a calendar sheet by mail. When no sheet was received, or when the sheet was completed incorrectly, we inquired by telephone whether

and when the participant had fallen in the past 3 months. Recurrent falling was defined as 2 or more falls within 6 months.<sup>10,11,24</sup>

### *Statistical analysis*

First, the main baseline characteristics and prevalences of the items of the fall risk profile in FPT and LASA were presented. Second, the goodness-of-fit was tested using the Hosmer-Lemeshow test in the multivariate logistic regression model ( $p > 0.05$  indicates a good fit). Third, in FPT, the predictive validity was examined by calculating the following diagnostic values for each cut-off point: percentage in high risk group (i.e. percentage of participants scoring the cut-off value or higher on the fall risk profile), sensitivity, specificity, sum of sensitivity and specificity, positive predictive value and negative predictive value. Fourth, the area under the ROC curve (AUC) and 95 % confidence interval (CI) were computed to evaluate the discriminative ability of the model. Finally, to examine whether the item fear of falling could be replaced by the question “Are you afraid to fall”, the AUC was recalculated using this measure. All analyses were conducted using SPSS software (SPSS Inc., version 15.0.0).

## **Results**

From the FPT, 408 participants with complete fall follow-up were included in the validation study. The mean age was 77.9 (Standard Deviation=7.1) years, 73.3 % was female and the median risk score was 6 (Interquartile Range=3-9) (Table 1). Within one year of follow-up, 76 participants (18.6 %) became recurrent fallers. Of the persons with incomplete follow-up, 18 could not be contacted, 14 refused further participation, and 9 died. These excluded persons ( $n=41$ ) were older ( $p=0.04$ ) and tended to score higher on the risk profile ( $p=0.08$ ) than the included participants, but did not differ with respect to sex or living situation. Of the 408 participants included in the analyses, 36 % reported 2 or more falls in the preceding year and 51 % reported fear of falling. The Hosmer-Lemeshow goodness-of-fit test was not significant ( $p=0.99$ ), indicating that the model fits the data well.

Per cut-off value, the percentages of persons in the high-risk group, sensitivity and positive predictive values are presented in Table 2. The maximum sum of sensitivity and specificity was found at a cut-off value of 8. At a cut-off value of 8, the sensitivity was 56.6 % (CI: 51.8-61.4), the specificity was 71.4 % (CI: 67.0-75.8), the positive predictive value was 34.1 % (CI: 29.5-38.7), and the negative predictive value was 85.6 % (CI: 82.2-89.0). Figure 2 shows the ROC curve for the FPT. The AUC was 0.65 (CI: 0.58-0.72), which indicates that 65 % of the random pairs of recurrent fallers and non-recurrent fallers would be discriminated correctly as high and low-risk, respectively. Measuring the item ‘fear of falling’ with the question ‘Are you afraid to fall?’ instead of the FES did not affect the discriminative ability of the risk profile (AUC: 0.65, CI: 0.58-0.72).

**Table 1.** Baseline characteristics and prevalence of the items of the LASA fall risk profile in the Fall Prevention Trial (FPT)

	Fall prevention trial
N	408
Age	77.9 (7.1)
Sex (% women)	73.3
LASA fall risk profile (range 0-30, median [IQR])	6 [3-9]
Enrollment via Emergency Department (%) <sup>†</sup>	89.5
Items of the fall risk profile (%)	
≥2 falls in the preceding year	36.0
dizziness regularly	9.1
functional limitations (>2)	5.6
grip strength (women ≤32 kg; men ≤56 kg)	40.2
body weight (women ≤62 kg; men ≤70 kg)	32.6
dogs or cats in household	14.5
fear of falling (Falls Efficacy Scale ≥1)	51.0
alcohol use >15 glasses per week	6.4
education ≥11 years	50.2
≥2 falls in preceding year x fear of falling	10.5
alcohol >15glasses x education ≥11 years	2.5

<sup>†</sup> Enrollment via Emergency Department or family physician

## Discussion

The aim of this study was to apply an existing fall risk profile to a sample of community-dwelling older persons who consulted their family physician or ED after a fall. Although the goodness-of-fit suggested that the model fitted the data well, the discriminative ability was moderate. Approximately 65 % of recurrent fallers and non-recurrent fallers were correctly classified as high or low risk of recurrent falling, respectively. The maximum sum of sensitivity and specificity was found at a cut-off value of 8.

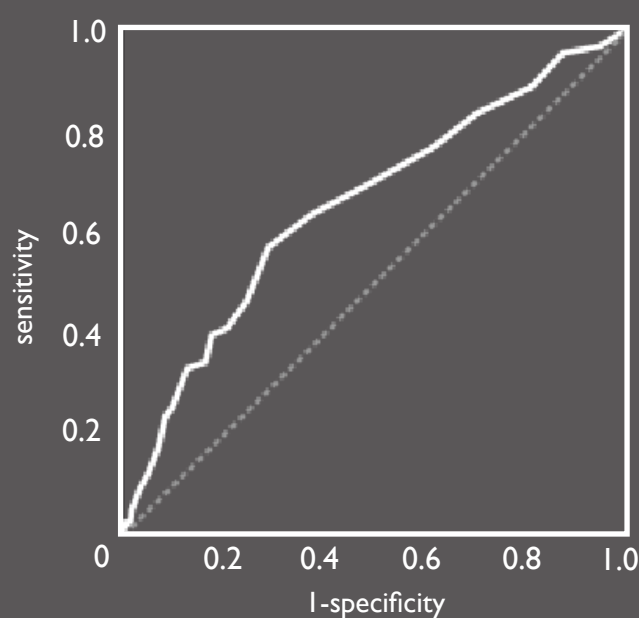
The high prevalences of the items two or more falls in the previous year and fear of falling emphasize that the current sample was indeed a population with an, on average, higher fall risk than in the LASA sample. This also becomes evident from the differences in recruitment. The LASA sample is a relatively healthy sample of the Dutch community-dwelling older population stratified for age, sex, and five years mortality rate, and no specific fall-related selection criteria were used.<sup>10</sup> The FPT sample, on the other hand, represents a population presenting after a fall at the ED or family physician within the vicinity of the VUmc. The differences between these samples became evident in the prevalences of the items, and consequently the different diagnostic values per cut-off value in FPT as compared with LASA, and lower discriminative ability (AUC in LASA: 0.71, CI: 0.67-0.74; AUC in FPT: 0.65, CI: 0.58-0.72).



**Table 2.** Diagnostic values of the LASA fall risk profile in the Fall Prevention Trial

Cut-off in total risk score	% at high risk group	Sensitivity (%)	Specificity (%)	$\Sigma$	PV+ (%)	PV- (%)
0 vs. $\geq 1$	94.1	92.4	6.3	98.7	19.0	87.5
0-1 vs. $\geq 2$	88.0	94.7	13.6	108.3	20.1	91.8
0-2 vs. $\geq 3$	81.9	88.2	19.6	107.8	20.1	87.8
0-3 vs. $\geq 4$	72.1	82.9	30.4	113.3	21.4	88.6
0-4 vs. $\geq 5$	64.0	76.3	38.9	115.2	22.2	87.8
0-5 vs. $\geq 6$	51.2	68.4	52.7	121.1	24.9	87.9
0-6 vs. $\geq 7$	42.2	63.2	62.7	125.9	27.9	88.1
0-7 vs. $\geq 8$	33.8	56.6	71.4	127.7*	34.1	85.6
0-8 vs. $\geq 9$	28.1	46.0	75.6	121.6	30.2	86.0
0-9 vs. $\geq 10$	24.3	40.8	79.5	120.3	31.3	85.4
0-10 vs. $\geq 11$	21.6	39.5	82.5	122.0	34.1	85.6
0-11 vs. $\geq 12$	19.6	34.2	83.7	117.9	32.5	84.8
0-12 vs. $\geq 13$	16.4	32.9	87.3	120.2	37.3	85.0
0-13 vs. $\geq 14$	12.5	25.0	90.4	115.4	37.3	84.0
0-14 vs. $\geq 15$	11.3	23.6	91.6	115.2	39.1	84.0
0-15 vs. $\geq 16$	8.8	17.1	93.1	110.2	36.1	83.1

$\Sigma$  Sum of sensitivity and specificity; \* maximum sum of sensitivity and specificity; PV+ Positive predictive value; PV- Negative predictive value

**Figure 2.** ROC Curve

The sensitivity on the y-axis is plotted against 1-specificity on the x-axis for the LASA fall risk profile in the Fall Prevention Trial. The area under the Receiver Operating Curve (AUC) is 0.65, CI: 0.58-0.72

Some of the predictors are susceptible to change (e.g. weight, grip strength) and thus the risk score may change over time. Consequently, the risk profile may be more accurate in predicting recurrent falling on the short term than on the long term. To test this, the diagnostic values and AUC were also calculated in the FPT with recurrent falling measured during 6 months of follow-up. As compared with one year of follow-up, the sensitivity and negative predicted values indeed were slightly higher and the specificity and positive predictive values were slightly lower (data not shown). The AUCs were similar after 6 and after 12 months of follow-up (6 months: AUC: 0.65, CI: 0.57-0.73). These results suggest that the predictive validity of the LASA fall risk profile is similar on the short term and on the long term.

Which cut-off value should be used depends on the purpose of the screening. On average, the optimal cut-off value is eight: at this value, the maximum sum of sensitivity and specificity was obtained. However, at this cut-off value the sensitivity was moderate resulting in a higher percentage of misclassification of recurrent fallers. If this risk profile is used to select persons who may benefit from preventive measures, it is important not to miss any of the recurrent fallers. To minimize misclassification, the sensitivity and negative predictive value should be high. Therefore, a lower cut-off value may be used, for example a cut-off value of five. Note however, that lower cut-off values do decrease the specificity and positive predictive values as a result of which too many persons will be referred to the prevention program. Internationally, fall prevention guidelines recommend multidisciplinary evaluation and tailored treatment of fall risk factors. Among low risk persons who are incorrectly classified as high risk and referred to a fall clinic, the evaluation will probably reveal fewer risk factors, and consequently the treatment will be simple and cheap. At very low cut-off values, too many persons will be referred to the prevention program and one may question the added value of screening prior to referral and the cost-effectiveness of the screening plus intervention.

The results of this study show that the discriminative ability of the LASA fall risk profile is not much higher than chance in persons who sought care after a fall. However, the discriminative ability in the current study was similar to that of the FROP-com, which was applied to a comparable population.<sup>13</sup> The FROP-com is a screening tool that consists of 26 questions and predicts the risk of falling.<sup>13</sup> The population of presenting fallers seems to be a relatively homogenous group, in which it is difficult to discriminate occasional fallers from recurrent fallers. Given the serious consequences of falling in older persons, each percentage gain in the discriminative ability is important. It would be interesting to compare the predictive validity of these risk profiles with clinical judgement and other risk profiles.

The strength of the LASA fall risk profile is its feasibility. After a short instruction, the profile is easy to administer. The time needed to complete the risk profile is approximately ten

minutes. Furthermore, few attributes are necessary (i.e. a balance beam scale and grip strength dynamometer). The profile can be further simplified by replacing the Falls Efficacy Scale (FES) with the question “Are you afraid to fall?”. A limitation of this study is that the results cannot be generalized to the general population. However, the current sample is a population in which case-finding for fall prevention is relevant. To evaluate the validity of this risk profile in different populations, further research is necessary. A second limitation is that 9 % of the participants had incomplete follow-up and had to be excluded from the analyses. These participants were older and scored higher on the fall risk profile. It is likely that the fall rate in this group would be higher which may have resulted in an underestimation of the discriminative ability in the FPT.

In conclusion, the discriminative ability of the LASA fall risk profile was moderate. The predictive validity of the LASA fall risk profile to identify recurrent fallers is limited among older persons who consulted the Emergency Department or family physician after a fall.

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1. How often did you fall during the past 12 months, including the last fall?

☐ <2 falls in the past 12 months (0 points)

☐  $\geq 2$  falls in the past 12 months (4 points) ..... points

2. Do you often have dizzy spells?

☐ no (0 points)

☐ yes (4 points) ..... points

3a. Are you able to use your own method of transport or public transportation?

☐ no (go to question 3b)

☐ yes (0 points, go to question 4)

3b. Are you able to go up 15 steps without standing still?

☐ no (go to question 3c)

☐ yes (0 points, go to question 4)

3c. Are you able to cut your own toenails?

☐ no (3 points when all three questions are answered with “no”)

☐ yes (0 points, go to question 4) ..... points

4. Grip strength right hand ..... kg (1)  
 ..... kg (2)  
 Maximum grip strength right hand: ..... kg

Grip strength left hand ..... kg (1)  
 ..... kg (2)  
 Maximum grip strength left hand: ..... kg

..... +

Total maximum hand grip strength ..... kg

female (total maximum grip strength):	male (total maximum grip strength):	
>32 kg (0 points)	>56 kg (0 points)	
≤32 kg (3 points)	≤56 kg (3 points)	..... points

5. Body weight (without shoes) ..... kg

female:	male:
>62 kg (0 points)	>70 kg (0 points)
≤62 kg (2 points)	≤70 kg (2 points)

..... points

6. Do you have a dog or a cat?

☐ no (0 points)

☐ yes (2 points) ..... points

7. How concerned are you that you might fall when:

	not at all 0	some- what 1	fairly 2	very 3
cleaning the house?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
getting dressed and undressed?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
preparing simple meals?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
taking a bath or shower?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
going to the shop?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
getting in or out of a chair?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
going up or down stairs?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
walking around outside?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
reaching up or bending down?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
answering the telephone?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Per question 0-3 points can be scored

Add up all the points: <1 (0 points)

≥1 (2 points)

..... points

8. Do you sometimes drink alcohol?

☐ no (0 points, go to question 9)

☐ yes

Do you drink alcohol every day? yes/no

How many days per week do you drink alcohol? ..... days/week

How many glasses of alcohol do you drink each time?

- during the week: ..... glasses

- during the weekends: ..... glasses

Total number of glasses per week: ..... glasses/week

(more than 15 glasses of alcohol per week = 1 point)

..... points

9. What is the highest level of education that you completed with a certificate?

☐ primary school (0 points)

☐ equivalent to junior high school, apprenticeship (0 points)

☐ high school, college, university (1 point)

(1 point is scored if 11 or more years of education completed)

..... points

10. Item 1: ≥2 falls in the past 12 months AND Item 7: ≥3 points (4 points)

..... points

11. Item 8: >15 glasses of alcohol AND Item 9: ≥11 years of education (4 points)

..... points

\_\_\_\_\_+

Total score on the LASA fall risk profile

.....



**A multifactorial intervention to reduce falls in older people at high risk of recurrent falls is ineffective; results of a randomised controlled trial**

Submitted as: OJ de Vries, GMEE Peeters, PJM Elders, M Muller, DL Knol, SA Danner, LM Bouter, P Lips. A multifactorial intervention to reduce falls in older people at high risk of recurrent falls is ineffective; results of a randomised controlled trial.



Opmerking van deelnemer op kalenderblad: "Ik probeer zo goed mogelijk te lopen, zodat mijn voeten in de knoop raken."

**Abstract**

**Context** Falls occur frequently in older people and have a strong impact on quality of life. Guidelines recommend multifactorial, targeted fall prevention programs for older persons with a high fall risk. Effectiveness of these programs is controversial.

**Objective** To evaluate the effectiveness of a multifactorial intervention in older persons with a high risk of recurrent falling.

**Design, Setting, and Participants** A randomised controlled trial of adults of 65 years and older who visited the Emergency Department of a university hospital or their family physician. Of 564 persons screened, 217 persons had a high risk of recurrent falls and were randomised into a multifactorial intervention group (n=106) and a usual care group (n=111). During the 1 year follow-up, all falls were registered weekly.

**Intervention** The targeted multifactorial fall prevention predominantly consisted of treatment of orthostatic hypotension, reduction of fall risk increasing drugs, muscle strength and balance training, and reduction of home hazards. The interventions were performed by a team of a hospital-based geriatrician, an occupational therapist and a geriatric nurse, the participants primary care physician and primary care based physical therapists.

**Main Outcome Measures** Primary outcome measures were time to first and to second fall after randomisation. Secondary outcome measures were activities of daily living, quality of life, and physical performance.

**Results** Within one year, 55 (52 %) intervention participants and 62 (56 %) usual care participants fell at least once. Intention-to-treat analysis showed no significant treatment effect on neither the time to first fall (hazard ratio (HR)=0.96, 95 % confidence interval (CI): 0.66-1.38) nor the time to second fall (HR=1.05, CI: 0.66-1.69). Similar results were obtained for secondary outcome measures and when compliant participants were compared with usual care.

**Conclusion** This multifactorial fall prevention program did not reduce falls in high-risk older persons.

Trial Registration Current Controlled Trials ISRCTN11546541

<http://www.controlled-trials.com/ISRCTN11546541>

## Introduction

Fall incidents occur frequently in older persons. Annually, about 30 % of persons older than 65 years falls at least once and 15 % falls at least twice.<sup>1-3</sup> The consequences of falling are severe: 5 % of the falls leads to a fracture and 5 % leads to other serious injuries.<sup>4,5</sup> About one in four fallers consults a hospital emergency room or primary care physician after the fall.<sup>5</sup> Other consequences are loss of function and mobility, fear of falling and increased institutionalisation.<sup>5</sup> These facts emphasize the necessity of measures to prevent falling in older persons.

The pathogenesis of falling is multifactorial.<sup>1,6</sup> The risk of falling is associated with impairments in balance, gait, muscle strength, visual acuity, cognition, chronic diseases, postural hypotension, and use of psychotropic medication.<sup>7-11</sup> Interventions to reduce the risk of falling have been successful to a varying degree. Home visits by nurses were found to be ineffective,<sup>12</sup> whereas Tai Chi, exercise therapy and multifactorial interventions seem to lower the incidence of falls.<sup>13-15</sup> Several guidelines for the prevention of falls in older persons have been developed.<sup>16,17</sup> These guidelines recommend a systematic assessment and multifactorial treatment of fall risk factors in independently living older persons with a high risk of falling. Previous trials investigating the effect of multifactorial prevention strategies report conflicting results.<sup>18-23</sup> Even the meta-analyses are inconclusive.<sup>24-26</sup>

Many geriatric outpatient clinics have recently started “multidisciplinary fall prevention services”. However, in selected older persons with a high risk of recurrent falling the effectiveness of such a multifactorial intervention program has not been conclusively demonstrated yet. Previous studies selected older persons according to history of falls or after identification of fall risk factors.<sup>12,15,18,22,23</sup> However, the persons who were thus selected are not necessarily at increased risk. To be able to identify older persons with a high fall risk, several risk profiles have been developed.<sup>3,27-30</sup>

In this randomised controlled trial we have studied the effects of a multidisciplinary intervention on fall risk in older persons with a high risk of recurrent falling using the fall risk profile developed in the Longitudinal Aging Study Amsterdam (LASA). The intervention consisted of a systematic assessment of the risk factors of falling and subsequent targeted individualised preventive measures.

## Methods

### *Study design and population*

The design of this study was published in detail elsewhere.<sup>31</sup> In short, this study is a randomised controlled trial (RCT) with one year follow-up (Figure 1). The Medical Ethics Committee of the VU University Medical Center (VUmc), Amsterdam, the Netherlands, has approved the study.

The study population consisted of persons of 65 years and over, who consulted the Emergency Department (ED) of the VUmc or their family physician between April 2005 and July 2007 after a fall. Inclusion criteria were living independently or in a residential home, living in the vicinity of the VUmc and having experienced a fall. Exclusion criteria were inability to sign informed consent, Mini Mental State Examination (MMSE)  $<24$ ,<sup>32</sup> inability to provide a fall history, fall due to a traffic or occupational accident, living in a nursing home, last fall  $>3$  months before randomisation and acute pathology requiring long-term rehabilitation, such as a stroke. Sample size calculation indicated that 57 participants were needed in both the intervention and control group (significance level of 0.05, a power of 80 %, and an expected difference in fall incidence of 50 %).<sup>18</sup> Taking into account a drop-out rate of 30 % a minimum of 82 participants per group was needed.

Potential participants were contacted and the participants who met all inclusion criteria were asked to participate. All participants signed informed consent. The validated LASA fall risk profile was used to select participants with a high risk of recurrent falling (score of 8 and higher).<sup>31</sup> Participants with a low-risk of recurrent falling were excluded from the RCT. Participants living in a residential home were right away assigned to the high-risk group, which is in accordance with the recommendations of the Dutch Institute for Healthcare Improvement (CBO) guideline.<sup>17</sup> Participants in the high-risk group were randomised into the intervention group or the usual care group. A block randomization with block size 4 was used. The block size was unknown to the interviewers.

### *Procedure*

All participants were visited at their homes by a trained interviewer within 3 months after the presenting fall. During the first home visit, the fall risk profile, fall history, cognitive functioning, medical history, medication use, independence in activities of daily living, quality of life, and physical performance were measured. All high-risk participants were asked to report falls during one year after randomization, using a fall calendar. One year after randomization and the first home visit, they were visited a second time to reassess the activities of daily living, quality of life, and physical performance. Furthermore, therapy and recommendation compliance and medication use were evaluated.

### *Intervention*

The multidisciplinary intervention started with a visit to the geriatric outpatient clinic. A multifactorial fall risk assessment was conducted aiming to identify modifiable fall risk factors. The assessment of fall risk factors and design of the treatment plan was based on the directives in the CBO guideline "Prevention of fall incidents in older persons".<sup>17</sup> The assessment consisted of a general medical and drug history, a fall and mobility history, and physical examination.

According to the recommendations of the CBO guideline, special emphasis was placed on signs and symptoms of potentially modifiable fall and fracture risk factors, such as postural hypotension, visual impairment, parkinsonism, osteoporosis, osteoarthritis, gait disorders, psychotropic and cardio-vascular drug use, and environmental hazards. When indicated, additional diagnostic tests were performed (e.g. laboratory tests or imaging). Prior to the start of the study a general treatment regimen aimed at reduction of the fall risk was composed in close collaboration with a representative of the regional family physicians. The multifactorial treatment could consist of several therapies and recommendations. In participants who used cardiovascular or psychotropic drugs, withdrawal was recommended when no current medical or psychiatric condition warranted continuing treatment with the drugs. Special emphasis was laid on the importance of discontinuation of benzodiazepine use. When 25-hydroxy vitamin D3 levels were below 50 nmol/l, treatment with a combination of calcium carbonate 500 mg and colecalciferol 400 IE was initiated. Postural hypotension was primarily treated with compression stockings for the lower legs. Every participant with a gait disorder was referred to a physical therapist for balance and strength exercises. A home visit aimed at home hazard reduction by an occupational therapist was offered to every participant with a gait disorder who did not report previous involvement of an occupational therapist. Referral to an ophthalmologist was initiated when the corrected visual acuity was less than 0.5 on the Snellen chart, and an optimally treated or not treatable eye disease was excluded. Referral to other medical specialists was initiated when deemed necessary, for example referral to a cardiologist in participants with new or uncontrolled arrhythmias. The family physician of the participant was contacted by telephone directly after the visit to the out patient clinic to discuss referrals to medical specialists and medication changes. The treatment plan was initiated by the geriatrician. Per participant each diagnosis was coded according to the International Classification of Diseases (ICD10) and all recommendations were documented.

### *Usual Care*

Usual care in the Netherlands after a fall mainly consists of treatment of the consequences of the fall. Although guidelines recommend differently, in primary care settings 'usual care' rarely includes systematic assessment and treatment of fall risk factors.

### *Measurements*

#### *Primary outcome measures*

At the first home visit the participants received a fall calendar. For the period of one year, the participants ticked per week whether they had fallen during that week. A fall was defined as an unintentional change in position resulting in coming to rest at a lower level or on the ground.<sup>33</sup> Both the time in days until first and until second fall were used as primary outcome measures. Participants who were lost to follow up or deceased were censored at the time of drop-out.

*Secondary outcome measures*

Level of independence in activities of daily living (ADL) was examined using the Barthel Index.<sup>34</sup> Instrumental ADL was examined using the scale developed by Lawton and Brody.<sup>35</sup> Quality of Life (QoL) was examined using the Dutch translations of the SF-12 and the EQ-5D (EuroQol).<sup>36,37</sup> To assess physical performance, three tests were conducted. The chair stands test is a standardized test in which the participants stands up and sits down for five consecutive times as fast as possible with the arms folded in front of the chest.<sup>38</sup> During the walk test the participant walks 3 meters up and down a line.<sup>38</sup> The tandem stance test (one foot in front of the other) was used as a measure for standing balance.<sup>39</sup> The scores on the three tests (range 0-4) were summed to a total physical performance score (range 0-12). In each secondary outcome, higher scores indicate better conditions.

*Other measurements*

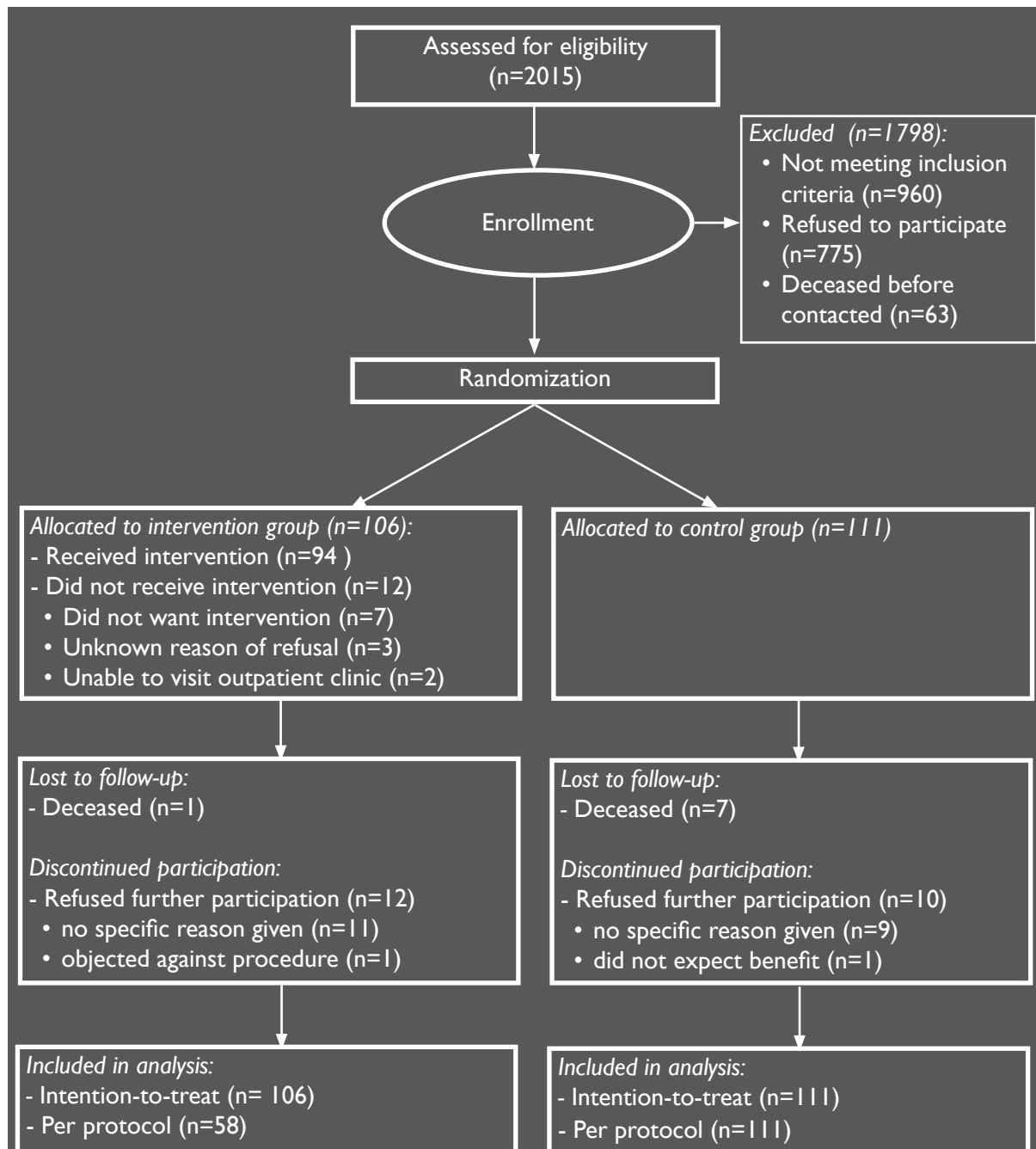
Medication use was assessed by directly copying the prescription information of drugs used in the previous two weeks from the containers. Living situation was assessed and categorized as independent versus living in a residential home. Self-reported number of seven major chronic diseases (i.e. lung diseases, cardiac diseases, vascular diseases, joint diseases, malignant deformities, diabetes mellitus, and stroke) was measured using a questionnaire on (chronic) diseases, both in the past and present. With questionnaires at 3, 6, and 12 months, all self-reported consultations and acquired aids and adaptations were documented. Finally mortality was documented.

*Compliance*

During the second home visit in the intervention group, adherence to the treatment regimen was evaluated per recommendation given. Adherence was assessed by asking whether the recommendations of the intervention were effected. Sufficient compliance was defined as completion of both an out-patient clinic visit and a second home visit, and adherence to at least 75 % of the recommendations, or in case of referral to exercise therapy, full adherence to exercise therapy and to 60 % of the remaining recommendations.

*Statistics*

Data were analysed according to the intention-to-treat principle, i.e. including all randomised participants, regardless of whether they did or did not receive the intervention. The results of the intention-to-treat analysis were compared with the results of the per-protocol analysis. Intervention participants included in the per-protocol analyses had fulfilled the sufficient compliance criteria. To examine the effectiveness of the intervention, Cox proportional hazards analyses were performed, with time to first fall and time to second fall as outcome variables. Subsequently, univariate linear regression analyses were used to compare differences in



**Figure 1.** Flow chart

secondary outcomes (ADL, QoL, and physical performance) at 12 months follow-up between the intervention and control groups. Per outcome measure, interaction of randomisation with sex was tested and if an interaction was found ( $p < 0.10$ ), further analyses were stratified for sex. Also, effect sizes were calculated (regression coefficients divided by the standard deviation (SD) of the total sample). Effect sizes greater than 0.30 and 0.80 suggest a medium and large effect, respectively.<sup>40</sup> Finally, the effect of the intervention on mortality was analysed using Cox proportional hazards model with time to death during one year of follow-up as the outcome measure.

Imputation of missing values on the secondary outcomes was done using the Multivariate Imputation by Chained Equations (MICE) algorithm.<sup>41</sup> The imputation model was used to explain the pattern of missing data and to obtain imputed values for these missing data, and included the following variables: group randomization, age, sex, education level, MMSE, number of chronic diseases and the fall risk profile score. Imputed values were based on regression estimates. Five imputed datasets were created. The quality of the imputations depends on the amount of missing data. When this does not exceed 50 %, 5 imputations are enough to obtain valid estimates.<sup>42</sup> The analyses were performed in each dataset and the results were pooled using the Rubins rules.<sup>43</sup> R software (version 2.7.2) was used to perform imputation, all other analyses were done using SPSS software (SPSS Inc., version 15.0).

## Results

In the inclusion period, 2015 persons of 65 years and older were identified with a presenting fall (Figure 1). Of these persons 775 did not wish to participate. Non-response analyses showed more women (76.4 versus 70.5 %) and ED presentations (96.2 versus 84.8 %) in the non-responders group. The inclusion criteria were not met by 960 persons, and 63 persons died before first contact. The remaining 217 persons were included in the trial. Randomization resulted in 106 participants in the treatment group and 111 in the control group. The baseline characteristics of the two groups were similar (Table 1). None of the participants had missing values on primary outcome measures. However, 20 intervention (18.9 %) and 27 control participants (24.3 %) did not have a second home visit, resulting in missing values on secondary outcome measures. Reasons for not having a second home visit were dropping out before visit (n=19), refusal (n=18), deceased (n=8), and other reasons (n=2).

The intervention participants visited the geriatric outpatient clinic after a mean of 47 days (SD 21.1) after the initial presentation at the ED or family physician. These 106 participants received a total of 351 recommendations (median=3 recommendations per participant, range 0-8). The recommendations included 176 referrals, 111 medication revisions, 52 instructions and 19 other recommendations (Table 2).

Self-reported consultations, medication changes and acquired aids and adaptations in both the intervention and usual care group are reported in Table 3. For the per-protocol analysis, 48 persons in the intervention group were excluded because they did not visit the outpatient clinic (n=12), did not or only partially follow therapeutic advice (n=23) or did not receive a second home visit (n=13). In total, 58 intervention participants (55 %) met our criteria for sufficient compliance and were compared to all usual care participants in the per-protocol analyses.



**Table 1.** Baseline characteristics of the intervention group (n=106) and control group (n=111)

	Intervention group	Control group
Age (mean (SD))	79.0 (7.7)	80.6 (7.0)
Sex (% women)	67.0	73.9
Living situation (% home for the elderly) <sup>†</sup>	3.8	4.5
Enrollment (% Emergency Department) <sup>‡</sup>	84.9	84.7
Education (% ≥11 years of education)	61.9	55.0
MMSE (median [IQR])	28.0 [26.0-29.0]	28.0 [27.0-29.0]
LASA fall risk profile (median [IQR])	12.0 [10.0-15.0]	12.0 [9.0-14.0]
Chronic diseases (median [IQR])	1.0 [0.0-2.0]	1.0 [1.0-2.0]
Number of medications (mean (SD))	5.8 (3.2)	5.8 (3.2)
Barthel Index (median [IQR])	19.0 [17.0-20.0]	19.0 [17.0-20.0]
Lawton IADL (median [IQR])	7.0 [5.0-8.0]	7.0 [5.0-8.0]
SF12 physical component (mean (SD))	38.1 (8.4)	37.7 (8.6)
SF12 mental component (mean (SD))	49.6 (11.0)	50.9 (10.3)
EuroQol (median [IQR])	0.78 [0.65-0.84]	0.78 [0.65-0.84]
Physical performance	7.0 (2.6)	6.4 (2.6)
Number of falls preceding year (median [IQR])	2 [2-4]	2 [1-3]

SD standard deviation; IQR Interquartile Range; MMSE Mini-Mental State Examination; IADL Instrumental Activities of Daily Living; <sup>†</sup> Living independently or in a home for the elderly; <sup>‡</sup> Enrolled via Emergency Department or family physician

**Table 2.** Specification of recommendations and adherence in the intervention group

Type of recommendation	Total number	Adhered to recommendation			
		yes	alternative <sup>†</sup>	no	?
Referrals	176	101	25	25	25
physical therapy	80	47	11	11	11
occupational therapy	30	17	5	5	3
ophthalmologist	20	10	1	3	6
cardiologist	11	8	1	0	2
other referrals	35	19	7	6	3
Medication	111	49	19	22	21
initiation Calcium/Vitamin D	19	11	3	4	1
discontinue benzodiazepines	17	6	5	4	2
other medication changes	75	32	11	14	18
Instructions	52	27	13	9	3
risky behaviour	8	4	1	3	0
reduce alcohol intake	10	4	3	2	1
other instructions	34	19	9	4	2
Mixed recommendations	19	10	2	4	4
use compression stockings	15	8	1	3	3
other recommendations	4	2	1	1	1
Total recommendations	358	187	59	60	52
% of recommendations		52.2	16.5	16.8	14.5

**Table 3.** Self-reported consultations, medication changes and acquired aids and adaptations in both the intervention and usual care group

	Intervention group (n=106)	Control group (n=111)
Consultations		
family physician	502	377
other physicians	284	200
physical therapy	678	502
occupational therapy	67	17
Medication changes		
initiate Calcium/Vitamin D	17	8
discontinue benzodiazepines	9	8
Aids and adaptations		
walking aids	56	57
home modifications	140	106

Questionnaires were completed 3, 6, and 12 months after baseline and covered the preceding 3, 3, and 6 months, respectively. Of the 651 questionnaires, 596 (92%) were completed. The presented numbers were based on the completed questionnaires. Home modifications vary from grips and shower seats to chair lifts and height-adjustable beds. Medication changes were assessed by comparing medication use at baseline with medication use at 12 months after baseline.

During one year of follow-up, 55 (52 %) intervention participants and 62 (56 %) control participants fell at least once and 37 (35 %) and 35 (32 %) participants fell at least twice respectively. The percentage of fallers and recurrent fallers did not differ significantly between intervention and control groups ( $p>0.55$ ). The median number of falls in the treatment group was 1 (Inter Quartile Range (IQR): 0-3), and in the control group also 1 (IQR: 0-2). Intention-to-treat analysis showed no significant treatment effect on the time to first fall (hazard ratio (HR) =0.96, 95 % confidence interval (CI): 0.67-1.37) nor on the time to second fall (HR=1.13, CI: 0.71-1.80) (Figure 2). The per-protocol analysis, in which 58 participants of the intervention group who met the criteria for compliance were compared to the control group, did not relevantly change the treatment effects (data not shown).

Analysis of secondary outcomes yielded no significant differences in longitudinal changes of (I)ADL, QoL, and physical performance (Table 4). Table 4 should be read as follows: the mean difference in Barthel Index between baseline and the follow-up measurement 12 months later is -0.23 in the intervention group, which suggests a slight decline in daily functioning, and 0.15 in the control group, which suggests a slight increase in daily functioning. The regression coefficient

**Footnote Table 2:**

†Alternative indicates that the participant took action in response to the recommendation, but did not exactly do what was recommended. For example, a participant was referred to the physical therapist, and went to the physical therapist, but did not do the home exercises or quit after a few sessions.

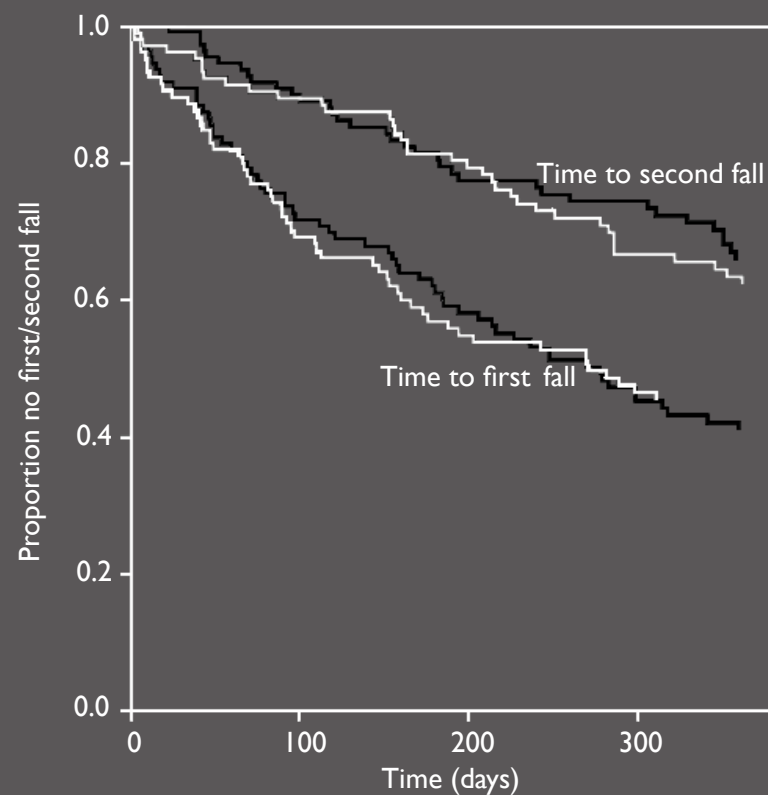


Figure 2. The time to first and second fall for the intervention and control groups. The proportion of participants who did not have a first or second fall yet is presented on the y-axis, the time in days is presented on the x-axis. The lower two lines represent the time to first fall, and the upper two lines represent the time to second fall for the intervention (black line) and control groups (white line), respectively.

indicates the difference between the two groups in mean differences and the confidence interval shows that the two groups do not significantly differ in difference-score in the Barthel Index (i.e. the confidence interval includes 0). Using Cohens criteria for effect sizes, the effect size of -0.08 suggests a small effect. It can be concluded that the two groups do not differ significantly in changes on the Barthel Index over 12 months time.

In the intervention group 1 participant died, compared to 7 in the control group. This difference was not statistically significant (HR=0.15, CI: 0.02-1.21).

**Table 4.** Linear regression analyses with secondary outcome measures

	Mean difference (SD)		regression coefficient	CI	Effect Size
	Intervention	Control			
Barthel Index (range 0-20)	-0.23 (2.24)	0.15 (1.90)	-0.17	-1.31 to 0.97	-0.08
Lawton IADL (range 0-8)					
women	0.10 (1.51)	-0.08 (1.48)	0.20	-0.89 to 1.29	0.13
men	-0.66 (2.03)	0.28 (1.93)	-0.95	-3.63 to 1.74	0.47
EuroQol (range 0-1)	0.01 (0.16)	0.07 (0.16)	-0.01	-0.30 to 0.29	-0.04
SF12 mental component (range 0-100)					
women	-1.34 (11.44)	-1.03 (10.48)	-0.56	-3.72 to 2.60	-0.05
men	1.79 (11.12)	-2.58 (9.55)	4.38	-7.65 to 16.40	0.41
SF12 physical component (range 0-100)	2.60 (8.60)	1.86 (8.83)	0.69	-2.15 to 3.53	0.08
Physical performance (range 0-12)	-1.12 (3.05)	-0.72 (3.40)	-0.36	-1.98 to 1.27	-0.11

Mean differences (follow-up - baseline) and Standard Deviations (SD) for the intervention and control groups are presented. Negative mean differences indicate a decline in the outcome measure. The crude regression coefficients and corresponding 95 % confidence intervals (CI) present the differences between the intervention and control group in difference scores. Effect sizes (regression coefficient/SD of total sample) greater than 0.30 and 0.80 suggest a medium and large effect, respectively.<sup>41</sup> All results were pooled over the five imputed datasets. IADL Instrumental Activities of Daily Living.

## Discussion

In our multidisciplinary falls prevention study, the selected high-risk patients did not benefit from the multifactorial intervention. The resulting risk of becoming a recurrent faller, the level of physical functioning, and quality of life did not differ from usual care. Several explanations for the lack of difference in outcome between the two groups are possible.

One explanation may be that after publication of several hallmark studies and guidelines on fall prevention, usual care has incorporated many beneficial strategies that are equally effective as a multifactorial intervention. This may have resulted in a lack of contrast between the groups. Received care in the control group, as shown in Table 3, illustrates the therapeutic response following a fall incident in usual care. When compared to the intervention group, the control group received 70 to 75 % of the number of sessions with physicians or physical therapists. The explanation is furthermore supported by the finding that patients from both the intervention and control group reported a higher fall rate in the year before the study than was measured during study follow-up ( $p < 0.001$ ): both the treatment and the control group reported a median of 2 falls in the preceding year (IQR: 2-4 and 1-3, respectively). The magnitude of the difference between the number of falls in the year preceding the study and the year of the study is probably even greater than measured, because the impact of recall bias is expected to be greater when falls are recorded retrospectively (year before study) as compared with prospective follow-up.<sup>44</sup>

Second, it may be that screening and telling patients about the aim of the study and their estimated fall risk is an effective intervention. Increased awareness of their high fall risk and precautionary measures such as avoiding dangerous situations may lower the incidence of falls considerably.

Third, the lack of effectiveness may be attributed to a too small study sample (type 2 error). An inverse power calculation with the current sample size and proportions demonstrated sufficient power to detect a difference of 19 % in the proportion of fallers and 17 % in the proportion of recurrent fallers. These findings render a type 2 error improbable.

Furthermore, by using the LASA fall risk profile to select high risk participants, we may have selected a population with shared characteristics that rendered a multifactorial intervention ineffective. However, more than 70 % (81 participants in both groups) of the included participants would also have been selected if we would have selected only on 2 or more reported falls in the previous 6 months. When the time to first and second fall was analysed of these 162 participants, the results did not change:  $HR > 0.90$ ,  $p > 0.60$ .

Finally, another possibility is that the kind of intervention that we offered is not adequate to lower the fall risk in the very high risk group that we selected. Especially physical therapy aimed at training balance and strength might have led to hazardous situations during and after therapy. Increased muscle strength might have preceded improvement of balance and endurance. Because the number of physical therapy consultations in the control group also is high (1662 and 1989 self-reported consultations in the control and intervention group, respectively) we performed a post-hoc evaluation in which we combined participants of both groups. Participants who had at least 3 physical therapy sessions were compared to those who did not. To control for the effect of confounding by indication we adjusted for gender and intervention. No significant difference was present in any of the other potentially confounding baseline characteristics. The fall risk was significantly elevated in the physical therapy group: HR for time to first fall=1.73, CI: 1.15-2.60, and HR for time to second fall=1.69, CI: 1.00-2.88. These findings are in accordance with a study which found that frail older persons who had exercise therapy had an increased fall risk as compared with control subjects,<sup>45</sup> which gives some support to our hypothesis about the dangers of physical therapy in the patients with the highest fall risk. On the other hand it is possible that our functional and other measurements did not reveal the apparent differences in vulnerability that made physicians decide which patient would benefit from a referral to physical therapy. A number of non-significant differences between the two groups might add up to clinically relevant differences in fall risk resulting in selective referral of the highest risk participants to physical therapy.

The principal outcomes of our study confirm previous findings and expert opinions feeding concerns about effectiveness of fall prevention in high-risk older persons.<sup>21,46</sup> Another recently published Dutch study attributed the lack of effectiveness of their fall prevention program to insufficient compliance, partly due to the organisation of the Dutch healthcare system.<sup>21</sup> In our study we achieved a much higher compliance rate, but this did not result in a positive outcome for the intervention group. Our study adds to the growing body of evidence that should urge national guideline developers to reconsider the recommendations in current fall prevention guidelines concerning community dwelling older persons at a high risk of falls.

The strength of our study is the selection of older persons with a very high risk of recurrent falls and with a high risk of fractures and loss of independence.<sup>28</sup> Being able to prevent falls in these patients is of the utmost importance. To achieve this we have tried to optimise the use of the relevant hospital and primary health care services that are routinely available in the Dutch healthcare system.

Limitations of our study result from limited resources in standard health care. To maximize the use of these resources and the compliance we were dependent on limited availability of primary care employees such as home care nurses and physical therapists. Furthermore we did not incorporate an intervention separately aimed at psychological components of fall risk like fear of falling. Programs to address fear of falling are not routinely available in the Netherlands. We assumed that regaining confidence through training of balance and strength would also have a positive effect on fear of falling. Lastly, the non significant difference in mortality between the intervention and the control group may be an indication of beneficial effects of our intervention that we have not been able to measure with the follow-up instruments that we have used.

Further studies aimed at fall risk reduction in older persons at high risk are urgently needed. We would especially recommend to study the effects of different kinds of physical therapy that are feasible in standard care. We postulate that training of balance and endurance should precede training of muscle strength. Furthermore, we think that compliance with the intervention can be further improved with intensified primary care-based encouragement and supervision, for instance by nurse-led home visit programs. Due to addictive properties of benzodiazepines the compliance with tapering and discontinuing these drugs is especially low. Home visits to support patients during discontinuing these drugs may be beneficial. Last but not least: giving older persons with a high risk of recurrent falls explicit information about their high fall risk should be an integral part of secondary fall prevention.

The conclusion that can be drawn from our study should be that current multifactorial fall prevention programs are not suited to reduce fall risk in older persons with the highest risk of falling. New intervention programs should be developed and tested in this target group. Until then, we recommend to stop applying the current multifactorial intervention to high-risk patients.



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**Multidisciplinary evaluation and treatment of persons with a high risk of recurrent falling was not cost-effective**

GME Peeters, M Heymans, OJ de Vries, LM Bouter, P Lips, MW van Tulder.

Interviewer: “Ik heb u nu alle vragen gesteld. Heeft u misschien nog vragen?”

Deelnemer (93 jaar): “Ja, waar blijft mijn AOW?”

**Abstract**

**Objective** International guidelines recommend multidisciplinary evaluation and tailored treatment of risk factors to reduce falling in older persons. The cost-effectiveness may be enhanced in high-risk persons. Our study evaluates the cost-effectiveness of multidisciplinary evaluation and treatment of fall risk factors in community-dwelling older persons at high risk of recurrent falling.

**Methods** An economic evaluation was conducted alongside a randomised controlled trial. Participants ( $\geq 65$  years) with a high risk of recurrent falling were randomised into an intervention ( $n=106$ ) and usual care group ( $n=111$ ). The intervention consisted of multidisciplinary assessment and treatment of fall risk factors. Clinical outcomes were proportions of fallers and utility during one year. Costs were measured using questionnaires at 3, 6, and 12 months after baseline and valued using cost prices, if available, and guideline prices. Differences in costs and cost-effectiveness were analyzed using bootstrapping. Cost-effectiveness planes and acceptability curves were presented.

**Results** During one year, 52 % and 56 % of intervention and usual care participants reported at least one fall, respectively. The clinical outcome measures did not differ between the two groups. The mean costs were Euro 7,740 (SD 9,129) in the intervention group and Euro 6,838 (SD 8,623) in the usual care group (mean difference Euro 902, bootstrapped 95% confidence interval: -1,534 to 3,357). Cost-effectiveness planes and acceptability curves indicated that multidisciplinary evaluation and treatment of fall risk factors was not cost-effective as compared with usual care.

**Conclusion** Multidisciplinary evaluation and treatment of persons with a high risk of recurrent falling was not cost-effective.

## Introduction

Fall incidents are the third cause of chronic disability in older persons according to the WHO.<sup>1</sup> One in three community-dwelling persons of 65 years and older falls once per year<sup>2-4</sup> and about 25 % of the fallers consult the family physician or Emergency department (ED) of a hospital.<sup>5-7</sup> The consequences may be severe and approximately 5 % of the falls result in a fracture.<sup>7,8</sup> In older persons consulting the ED after a fall, the average total costs from the moment of the fall to one year later have been estimated at Euro 4,991.<sup>9</sup> Because of the increasing number of older persons in the next decades, the number of fallers is expected to rise. Preventive measures are needed to reduce the number of falls and related costs. Although many trials have evaluated the effectiveness of preventive interventions, few have evaluated the cost-effectiveness of these interventions.

Over the past decades, many randomised controlled trials (RCTs) have studied the effectiveness of multifactorial interventions, i.e. multidisciplinary evaluation and treatment of fall risk factors.<sup>10-18</sup> Despite conflicting results among original trials, meta-analyses seem to favour multifactorial interventions.<sup>19-21</sup> Although the evidence does not seem to be conclusive, international guidelines recommend multidisciplinary evaluation and tailored treatment of fall risk factors.<sup>8,22</sup> Increasing numbers of geriatricians initiate fall prevention programs based on these guidelines. Given the large number of fallers, evaluation and treatment of every older person after a fall is not feasible. It may be more cost-effective to limit the intervention to older persons with the highest fall risk.<sup>23</sup>

To our knowledge, only two studies have focused on the cost-effectiveness of multifactorial interventions among community-dwelling older persons. The first study was conducted in the US and found that the intervention was more cost-effective than usual care and this effect was the largest in the high risk group.<sup>24</sup> The second study found that the evaluation of fall risk factors by a geriatrician and occupational therapist was not cost-effective as compared with usual care in the Netherlands.<sup>9</sup> However, the first study did not include patient costs (e.g. informal care and self acquired aids and adaptations), and in the second study the compliance rate was low and the patients were not screened for fall risk.<sup>25</sup>

Our study aims to evaluate the cost-effectiveness of multidisciplinary evaluation and treatment of fall risk factors in community-dwelling older persons with a high risk of recurrent falling. Although the costs of the intervention are additional to the costs of usual care (i.e. treatment of the consequences of a fall), if proven effective, the intervention may lead to a reduction in falls and, consequently, in the direct medical costs of future falls.

## Methods

The study was designed as an economic evaluation alongside a randomised controlled trial (RCT). The study protocol was approved by the Medical Ethics Committee of the VU University Medical Center, Amsterdam, the Netherlands. The design of this study was described in detail elsewhere.<sup>26</sup> This paragraph summarizes the details that are relevant for this paper.

### *Study population*

The study population consisted of 2,015 persons of 65 years and older, who consulted their family physician or the ED of the VU University Medical Center, (VUmc) Amsterdam, the Netherlands, after a fall accident between April 2005 and July 2007. Inclusion criteria were living independently or in a residential home, living in the vicinity of the VUmc and having experienced a fall less than 3 months ago. Exclusion criteria were inability to sign informed consent, inability to provide a detailed history, fall due to a traffic or occupational accident, living in a nursing home and acute pathology requiring long-term rehabilitation such as a stroke. During the first home visit within 3 months after the presenting fall, the risk of recurrent falling was assessed using the validated LASA fall risk profile in 600 participants.<sup>27</sup> After the first home visit, 36 participants did not meet the inclusion criteria and were excluded (Figure 1). Participants who scored 7 points or lower on the LASA fall risk profile were considered at low risk of recurrent falling and were excluded from the RCT and economic evaluation (n=347). Participants with a risk score of 8 or higher and participants living in a residential home were considered to be at high risk of recurrent falling (n=217). These high-risk participants were randomly allocated to the intervention (n=106) and usual care groups (n=111). All participants signed informed consent.

### *Intervention*

The multidisciplinary transmural intervention started with a visit to the geriatric outpatient clinic. A multifactorial fall risk assessment was conducted by the geriatrician to identify modifiable fall risk factors. The assessment of fall risk factors and the design of the treatment plan were based on the Dutch Institute for Healthcare Improvement (CBO) guideline "Prevention of fall incidents in older persons".<sup>8</sup> The assessment consisted of a general medical history, a fall and mobility history, and physical examination with special emphasis on signs of postural hypotension, neurological deficits, visual disturbances, gait and mobility disorders, and medication. Additional diagnostic tests were performed if indicated (e.g. laboratory tests or imaging). Based on the assessment of fall risk factors, an individually tailored treatment regimen aimed at reduction of the fall risk was composed in collaboration with the family physician of the participant. The multifactorial treatment consisted of, for example, withdrawal of psychotropic drugs, balance and strength exercises by a physical therapist, home hazard reduction by an occupational therapist or referral to an ophthalmologist or cardiologist.

*Usual care*

During the study period, usual care after a fall in the Netherlands mainly consisted of treatment of the consequences of the fall. Although a national guideline was released in 2004,<sup>8</sup> multifactorial fall prevention had not been implemented yet by family physicians or at EDs.

*Outcome measures*

Clinical outcome measures of the economic evaluation were the prevalence of fallers and recurrent fallers and utility (quality of life). All participants reported falls during at least one year using a fall calendar.<sup>4</sup> The participants ticked per week whether they did or did not fall. Once per 3 months the participants returned a calendar sheet by mail. When no sheet was received, or when the sheet was completed incorrectly, we inquired by telephone whether and when the participant had fallen in the past 3 months. A fall was defined as an unintentional change in position resulting in coming to rest at a lower level or on the ground.<sup>28</sup> Recurrent falling was defined as having fallen twice or more within a 6-month period.<sup>27</sup>

Utility was assessed at baseline and after one year using the EuroQol (EQ-5D).<sup>29</sup> This questionnaire was developed to generate a general index of experienced health. Health states were estimated using reference values from a representative Dutch sample (range 0, death, to 1, optimal health).<sup>30</sup> Quality Adjusted Life Years (QALYs) were calculated as the area under the curve, with straight-line interpolation between utility at baseline and one-year follow-up.

*Costs*

The economic evaluation was conducted from a societal perspective. Health care costs (e.g., geriatrician consult, family physician care, specialist care, therapy, medication, hospitalisation, and nursing home admittance), patient and family costs (e.g. informal care), and costs in other sectors (e.g. medical devices, home modifications, and transportation aids) were included (for more details, see Table 3). The participants received a cost-evaluation questionnaire 3, 6, and 12 months after the first home visit. The 3- and 6-months questionnaires were sent by mail, the 12-months questionnaire was assessed by a research assistant during a second home visit one year after baseline. Health care costs were valued using the guideline prices published for the Netherlands.<sup>31</sup> The costs of medication use were estimated based on the medicine use reported during the first home visit at baseline and the second home visit after 12 months. Participants were asked which medications (both over the counter and prescribed drugs) they had used during the previous 2 weeks. Generic names and doses were copied directly from the containers. Also, the frequency and dose per intake were reported. Since the number of units taken during the year of follow-up was not known, an estimation was made based on the available information and the following assumptions: 1) medicine for chronic use reported at both home visits = frequency x 365 days; 2) medicine for chronic use reported at one home visit = frequency x 0.5 x 365 days;

3) medicine for temporary use = frequency x 0.5 x recommended duration; 4) medicine for incidental use = 10 % from the number of units in case of chronic use; 5) for participants who dropped out before the second home visit, the number of units was estimated based on half the number of days until drop out. In the second, third, and fifth assumption, it was unknown how long the participant had been taking a medication on the time point of assessment. Therefore 0.5 times the expected total duration was believed to be the overall best estimated duration. Information on recommended duration of medications was obtained from the pharmaceutical guidelines published by the Dutch Health Insurance Board (CVZ).<sup>32</sup> The prices per medication were obtained from the Royal Dutch Society of Pharmacy.<sup>33</sup> Costs of health care devices, aids and adaptations were estimated by asking retail prices from three suppliers in the Netherlands. For each product, the average price was used. All costs were expressed in 2007 Euros.

### *Statistical methods*

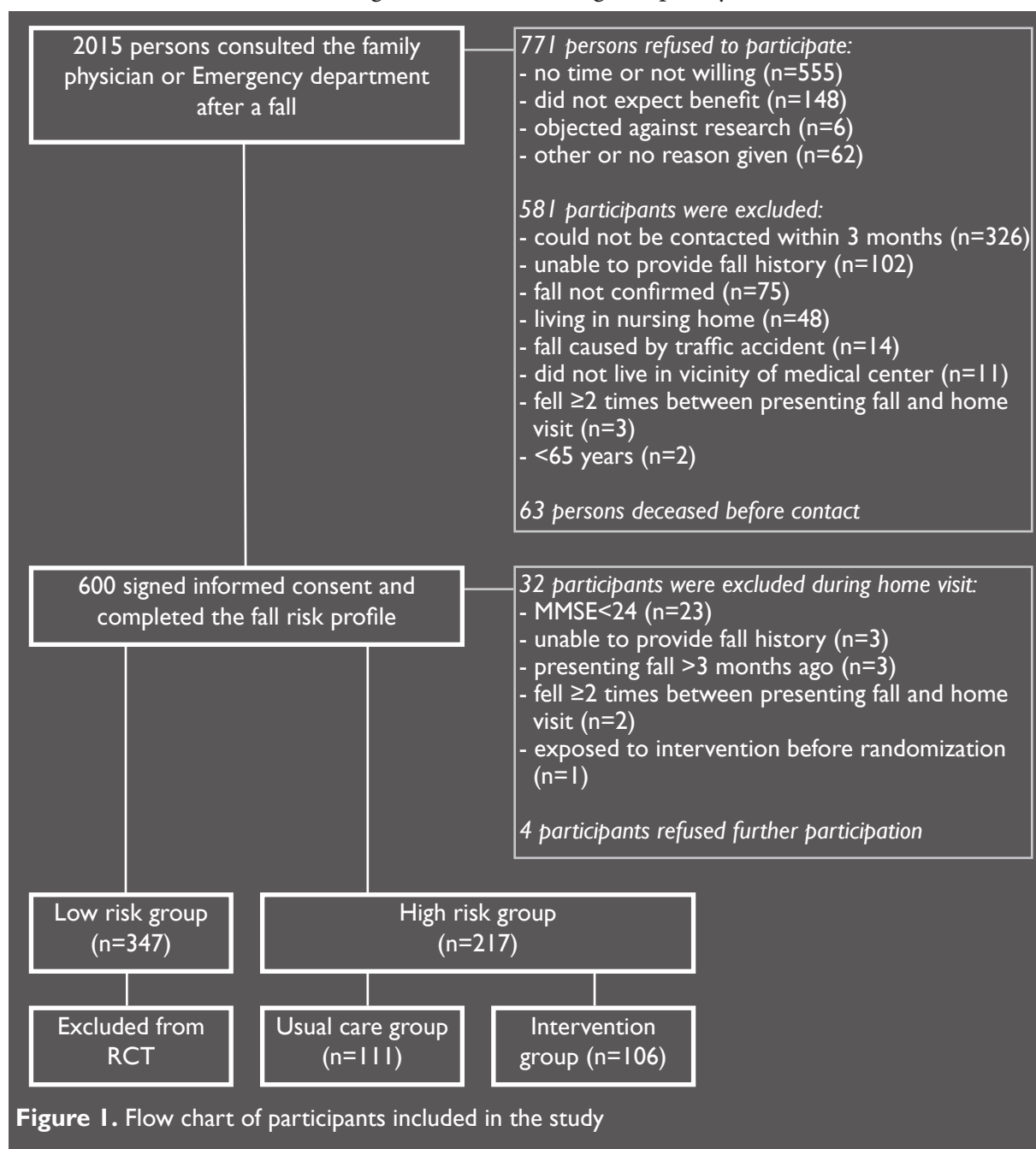
Baseline characteristics were estimated for the intervention and usual care groups. The economic evaluation was performed according to the intention-to-treat principle. The incremental costs and effects of the multidisciplinary transmural intervention were compared with usual care. Imputation of missing values was done using the Multivariate Imputation by Chained Equations (MICE) algorithm.<sup>34</sup> The imputation model, which was used to explain the missingness mechanism and to estimate the imputed values, included the variables group randomisation, age, sex, education level, Mini-Mental State Examination (MMSE), number of chronic diseases and score on the fall risk profile. According to the variables in the imputation model, imputed values were based on regression estimates. Imputation of cost variables was done before multiplying volumes by cost prices. For medication, the total costs were imputed. Five imputed datasets were created. The quality of the imputations depends on the amount of missing data. When this does not exceed 50 %, as in our study (approximately 10 %), 5 imputations are enough to get valid cost estimates.<sup>35</sup> The analyses were done in each dataset and presented are the pooled results of the 5 imputed datasets as described below.

Arithmetic mean (standard deviation, SD) costs were computed for both groups. Means and differences in costs and effects were estimated in each imputed dataset and results were combined using the Rubin's rules.<sup>36</sup> Mean difference between groups and the associated bias-corrected and accelerated confidence intervals were calculated using bootstrapping techniques. Bootstrap analyses to construct bias corrected accelerated confidence intervals were done in each imputed dataset and results were pooled.<sup>37</sup>

The economic evaluation involved estimating incremental cost-effectiveness ratios (ICER) of the incremental costs per avoided faller and recurrent faller. Also, an incremental cost-utility ratio (ICUR) was estimated for the incremental costs per QALY. ICERs and ICUR were



estimated by dividing the difference in costs by the difference in effects (ICER) or utility (ICUR) (intervention minus usual care) using bootstrapping techniques. Uncertainty around the ratios was graphically represented on a cost-effectiveness plane. The cost-effectiveness ratios presented on the cost-effectiveness planes were generated after bootstrapping of the imputed datasets. Cost-effectiveness acceptability curves were estimated to indicate the probability that the multidisciplinary transmural intervention was cost-effective given a ceiling ratio (i.e. maximum costs) that policymakers are willing to invest. To evaluate the influence of the missing values and their substitution by using multiple imputation techniques we performed a sensitivity analysis. In this way we were able to study the influence of missingness on the precision of the study results and check whether missing values were missing completely at random.



## Results

Of the 2,015 persons who consulted the ED or their family physician after a fall, 613 were excluded, 775 did not want to participate, 63 died before contact could be made, and 347 were assigned to the low risk group leaving 217 participants to be randomised into the intervention and usual care groups (Figure 1). The persons who refused to participate were more often contacted via the ED ( $p < 0.001$ ), but did not differ from participants in age or sex ( $p \geq 0.08$ ). Of all 217 participants included in the analyses, 8 died (3.7 %) and 22 dropped out (10.1 %) during follow-up. In total, 165 participants (76.0 %) had complete fall follow-up.

The groups were similar at baseline with regard to potential confounding factors (Table 1). The average age was 79.0 years (SD 7.7) in the intervention group and 80.6 years (SD 7.0) in the usual care group. The percentages of women were 67 in the intervention group and 74 in the usual care group. The median utility at baseline was 0.78 (Interquartile range 0.65-0.84) in both groups. The numbers of fallers during one year of follow-up were 55 (52 %) and 62 (56 %), and the numbers of recurrent fallers were 37 (35 %) and 35 (32 %) in the intervention and usual care groups, respectively (Table 2). In addition, the difference in QALYs gained over one year of follow-up between the intervention and usual group was small and not statistically significant.

**Table 1.** Baseline characteristics

	Intervention group (n=106)	Control group (n=111)
Age (mean (SD))	79.0 (7.7)	80.6 (7.0)
Sex (% women)	67.0	73.9
Education (% $\geq 11$ years of education)	61.9	55.0
Living situation (% home for the elderly) <sup>†</sup>	3.8	4.5
Baseline utility (EQ-5D) (median [IQR])	0.78 [0.65-0.84]	0.78 [0.65-0.84]
Number of falls preceding year (median [IQR])	2 [2-4]	2 [1-3]

SD standard deviation; IQR Interquartile Range; <sup>†</sup> Living independently or in a home for the elderly

**Table 2.** Clinical outcomes at 12 months and incremental cost-effectiveness ratios

	Intervention group	Usual care group	Difference	CI	ICER
% Fallers	52	56	-4.0	-17 to 9	226
% Recurrent fallers	31	28	3.2	-9 to 15	-280
Mean (SD) QALY	0.76 (0.11)	0.76 (0.14)	-0.004	-0.021 to 0.029	-232,533*

Presented are the pooled mean differences and 95 % Confidence Intervals (CI) in the clinical outcome measures and Incremental Cost-Effectiveness Ratios (ICER).\*) Incremental Cost-Utility Ratio.

The total mean costs were Euro 7,740 (SD 9,129) in the intervention group and Euro 6,838 (SD 8,623) in the usual care group (Table 3). The intervention and usual care groups did not differ in total costs (Euro 902; CI: -1534 to 3357). Also, the mean health care costs and the mean patient and family costs did not differ significantly between the groups (Table 3). Figure 2 shows the cost-effectiveness planes for the intervention group in comparison with the usual care group for the outcomes fallers, recurrent fallers, and QALYs gained. In all three planes, the cost-effect pairs cluster around the origin, indicating neither large nor significant differences in costs and effects. The percentage of fallers was 4.0 % lower in the intervention group as compared with the usual care group and the costs were Euro 902 higher, resulting in an incremental cost-effectiveness

**Table 3.** Mean health care, patient and family and total costs in Euros in the intervention and usual care groups

	<b>Intervention (n=106)</b>	<b>Usual care (n=111)</b>	<b>Bootstrap 95 % CI</b>
<i>Health care costs</i>	5995 (8399)	4858 (7606)	-1091 to 3371
- family physician <sup>1</sup>	167 (242)	136 (144)	-12 to 101
- hospital-related <sup>2</sup>	2195 (4755)	1720 (3950)	-672 to 1741
- paramedic and alternative medicine <sup>3</sup>	894 (1067)	644 (861)	-8 to 526
- formal care <sup>4</sup>	1369 (4338)	1614 (5827)	-1945 to 980
- medication <sup>5</sup>	1370 (4870)	745 (685)	64 to 2655
<i>Patient and family costs</i>	404 (695)	409 (1079)	-339 to 207
- informal care <sup>6</sup>	313 (682)	310 (1080)	-298 to 217
- other costs <sup>7</sup>	90 (111)	99 (91)	-37 to 23
<i>Costs in other sectors</i>	1332 (2203)	1566 (3285)	-1133 to 445
- transportation <sup>8</sup>	413 (1202)	739 (2623)	-1137 to 241
- health care devices, aids, adaptations <sup>9</sup>	843 (1543)	759 (1613)	-355 to 538
<i>Total costs</i>	7740 (9129)	6838 (8623)	-1534 to 3357

Presented are pooled means (standard deviations) and the bias corrected and accelerated bootstrapped 95 % Confidence Intervals (CI) in Euros.

<sup>1</sup> Family physician consultations (including telephone consultations and home visits)

<sup>2</sup> Specialized physician consultations (e.g. ophthalmologist, internal physician, geriatrician), Emergency department consultations, hospital admittance, and surgeries

<sup>3</sup> Consultations of physiotherapist, occupational therapist, and other therapists, and alternative medicine

<sup>4</sup> Home care (i.e. housekeeping, personal care, meal preparation, preparation and administration of medications, and wound care), day care, and admittance to nursing home or home for the elderly

<sup>5</sup> Over the counter and prescribed drugs

<sup>6</sup> Care received from family, neighbours, and friends

<sup>7</sup> Pedicure, and exercise programs (other than physiotherapy)

<sup>8</sup> Wheelchair, platform scooter, handicapped parking placard, and bicycle

<sup>9</sup> Rollator, crutches, walking stick, zimmer frame, orthopaedic shoes, brace/splint, compression stocking, hip protector, incontinence products, personal alarm, glasses, hearing aids, handrails, removing thresholds, smoothing surfaces, ramp, stair lift, replacing bathtub by shower, shower seat, (anti-slip) floor covering, electric door opener, high toilet, toilet arm rests, toilet chair, bath seat/lift, bath mat, raised chair, rise chair, working chair, bed raisers, height adjustable bed, and bed triangle

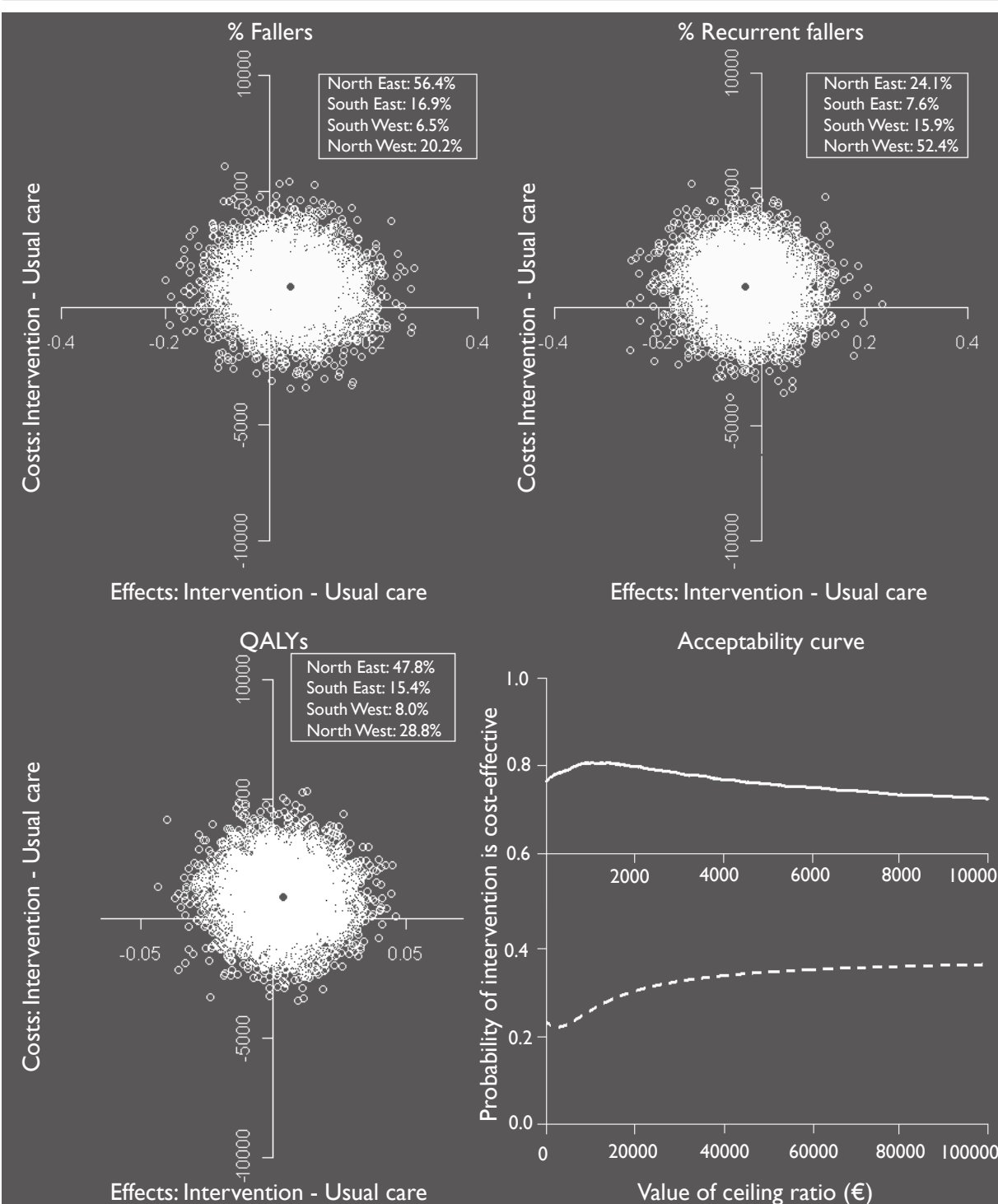
ratio (ICER) of 226. In other words, the costs per percentage decrease in fallers are 226 Euros. Since the percentage of recurrent fallers was higher in the intervention than in the usual care group, the ICER for recurrent falling was negative (ICER=-280). The acceptability curves show that the maximum probability of cost-effectiveness with respect to the proportion of fallers was obtained at a ceiling ratio of Euro 10,000 (Figure 2). This indicates that if Euro 10,000 were invested, the probability that the intervention would reduce the percentage of fallers by one percent was 0.80. Likewise, if Euro 300,000 were invested, the probability that the intervention would improve the quality of life (utility) by one point was only about 0.30. Since the costs were higher and effects were smaller for the outcome recurrent fallers, the intervention was not cost-effective at any given ceiling ratio and therefore this curve was not included in Figure 2.

To test the impact of imputation, the analyses were repeated with the 73 and 74 participants in the intervention and usual care groups, respectively, who returned all three cost-evaluation questionnaires and had complete data on medication and utilities. The total costs in the intervention group were Euro 220 lower than in the usual care group, however, this difference was not statistically significant (bootstrapped CI: -2,754 to 2,224). Since the percentage of fallers and recurrent fallers did not differ between the groups, the cost-effectiveness ratios clustered around the origin. ICERs were 116 for fallers, -120 for recurrent fallers and 23,044 for QALYs (data not shown).

## Discussion

This study investigated the cost-effectiveness of multifactorial evaluation and treatment of fall risk factors in persons with a high risk of recurrent falling. The intervention did not reduce the fall risk as compared with usual care during one year of follow-up. Explanations for a lack of differences in fall risk between the two groups have been described in Chapter 8. The average costs made from a societal perspective in persons with a high risk of recurrent falling who received the multidisciplinary intervention was Euro 7,740 in one year, which was Euro 902 higher than in the control group that received usual care.

The mean costs of participants who received the intervention were somewhat, but not statistically significant, higher than in participants who received usual care. Closer inspection of the costs per category reveals that medication costs were higher in the intervention group and these participants also tended to have higher costs of allied health care. Revision of medication was a facet of the intervention: 24 % of the participants in the intervention group were recommended to reduce or stop some medications while 33 % of the participants were recommended to start using certain medications. The costs per unit of the stopped medications (mostly psychopharmaca) were lower than the costs per unit of the started medications (mostly osteoporosis medication). This, in combination with the net rise in number of medications, may explain the higher costs



**Figure 2.** Cost-effectiveness planes and acceptability curves for the multidisciplinary evaluation and treatment of fall risk factors in comparison with usual care.

Cost-effectiveness planes are presented for a decrease in percentage of fallers (top left), for a decrease in percentage of recurrent fallers (top right), and for an increase in utility (QALY) (bottom left) after 1 year of follow-up. The panels in the cost-effectiveness planes display the percentages of estimated ratios per quadrant of the plane. North East quadrant: intervention is more effective and more expensive; South East quadrant: intervention is more effective and less expensive; South West quadrant: intervention is less effective and less expensive; North West quadrant: intervention is less effective and less expensive. The acceptability curves (bottom right) present the probability of the intervention being cost-effective as compared with usual care at various ceiling ratios of costs for fallers (solid line) and QALYs (dashed line).

in the intervention group. The higher costs of allied health care were anticipated, because 81 % of the participants in the intervention group were referred to the physiotherapist and/or occupational therapist.

Two previous studies have evaluated the cost-effectiveness of multifactorial fall prevention programs. Both our study and a recently published study which was conducted in Maastricht, the Netherlands did not show a difference in either costs or effects between the intervention and usual care groups.<sup>9</sup> The total costs in our study were somewhat higher than in the Maastricht study. However, in the Maastricht study all patients who consulted the ED after a fall were considered at high risk of falling, while we screened these patients to select those with a high risk of recurrent falling. Consequently, our sample was older and had a higher fall risk. In addition, the intervention participants in our study received more recommendations per person and the compliance rate was higher.<sup>25</sup> Finally, they expressed costs in 2004 Euros, whereas we expressed costs in 2007 Euros (1.0452 % inflation from 2004 to 2007). In 1996, a similar study was conducted in New Haven, Connecticut.<sup>24</sup> In this US study, the multifactorial targeted prevention program reduced the fall rate by almost 50 % and the costs by 26 % in participants with a high fall risk. However, two differences should be emphasized: first, the US study did not include patient and family costs, and second, usual care more often includes home modifications in the Netherlands than in the US. In the Netherlands, municipalities are responsible for their inhabitants to live as safely and independently as possible in their own environment and financial resources are available to improve the home environment for people who are disabled.

In the literature, it has been hypothesized that the cost-effectiveness of multifactorial evaluation and treatment of fall risk factors may be improved by selecting persons with a high risk of falling.<sup>23</sup> The current results do not support this hypothesis. Over the past few years, many geriatricians have initiated fall clinics with multifactorial preventive programs in the Netherlands. However, both the current study and the Maastricht study showed that this approach reduces neither the fall rate nor the costs among high-risk patients, and is thus not superior to usual care in the Netherlands. It is recommended that multifactorial evaluation and treatment of fall risk factors in older persons with a high fall risk should not be implemented in the Netherlands.

Some limitations of this study need to be pointed out. First, only 150 persons completed all three cost-evaluation questionnaires. Participants who did not return all questionnaires were older and frailer, and it is likely that the costs among these persons are higher. However, the proportions of missing questionnaires did not differ between the intervention and usual care groups. The total mean costs per group may be underestimated, but not the difference in costs. Second, the medication costs were estimated based on the assumptions described in the method. These assumptions introduce uncertainty in the estimation of the total costs and consequently the

incremental cost-effectiveness ratios. However, the same assumptions were used in both groups. Furthermore, repeating the analyses without the medication costs resulted in a smaller difference in the total costs between the two groups, and thus a smaller ICER. Third, imputation of missing values introduces extra uncertainty in the estimation of the effects. However, sensitivity analyses among persons with complete data revealed that the impact of imputation did not alter the results. Finally, we did not measure the costs in the low risk group. Thus, no conclusions can be drawn with respect to the costs or cost-effectiveness of the screening for risk of recurrent falling.

In conclusion, the multifactorial evaluation and treatment of fall risk factors was not cost-effective in persons with a high risk of recurrent falling. This fall prevention program should not be implemented in the Netherlands.



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# 10

## General Discussion

Questions rise and answers fall,... insurmountable.

A line from the song 'Love boat captain', composed by Eddie Vedder and Boom Gaspar, performed by Pearl Jam on the album 'Riot act'.

## General Discussion

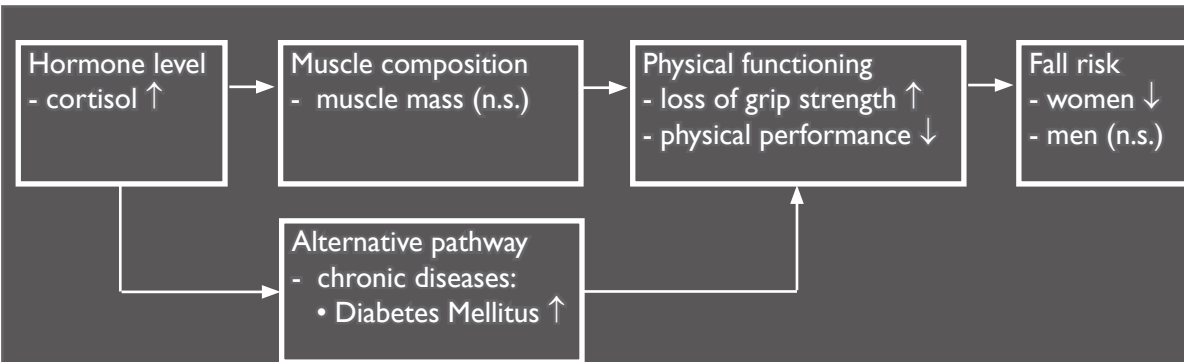
The subject of this thesis is prevention of falling in older persons with a high risk of recurrent falling. In this chapter, the main findings of this thesis will be discussed and an overall conclusion will be given. In addition, recommendations for future research and clinical practice are provided.

### The role of cortisol in fall risk factors

As described in the general introduction, high levels of cortisol caused by Cushing's disease or use of glucocorticoids are associated with muscle weakness. We studied whether similar relationships exist between the upper range of endogenous cortisol levels and physical outcome measures in a general population of older persons. We found that high levels of cortisol were associated with lower physical performance (*Chapter 2*). This association could be mainly explained by balance in women and proximal leg strength in men. In the next chapter (*Chapter 3*), we reported that high levels of salivary cortisol were associated with an increased risk of loss of grip strength. Lack of significant associations between serum cortisol and muscle mass and muscle strength may be due to the sensitivity of serum levels to daily fluctuations, nutrition and stress, and to differences in genetic background between the participants. Genetic studies suggested that the ER22/23EK and N363S polymorphisms of the glucocorticoid receptor gene might indeed modify these associations (*Chapter 3*). However, the associations found may be due to chance as a result of multiple testing, and validation of these findings in other studies is needed.

The association between cortisol and physical performance may be explained via various pathways, one of these being via alterations in muscle characteristics. If this theory is true, the association between cortisol and physical performance should be no longer significant after adjustment for muscle strength. After adjustment for muscle strength, the association between cortisol and physical performance remained significant, both in women and men. Thus, variation in muscle strength does not seem to explain the association between cortisol and physical performance. A second potential pathway may be via chronic diseases and diabetes mellitus (DM) in particular. Persons with high cortisol levels had higher risks of DM (*Chapter 4*) and DM patients are known to have poorer levels of physical functioning<sup>1-3</sup> and increased fall risks.<sup>4,5</sup> However, after additional adjustment for DM, the associations between cortisol and physical performance remained significant and the regression coefficients were similar. These results indicate that DM does not seem to explain the association between cortisol and physical performance. Alternative pathways may include neuronal or cognitive processes. Figure 1 summarises these results.

Poor physical performance has not only been associated with high levels of cortisol, but also with an increased risk of recurrent falling.<sup>6</sup> High levels of cortisol also may be associated with



**Figure 1.** The potential pathway from cortisol to fall risk  
n.s. not significant

an increased fall risk. Table 1 shows the results from the additional analyses. Women with high serum cortisol levels tended to have a 40 to 50 % lower risk of recurrent falling than women with low levels. In men, however, the association between serum cortisol and recurrent falling was not significant. An explanation of the lower fall risk in women with high levels of cortisol may be that low levels of cortisol have been associated with postural hypotension,<sup>7</sup> which is a risk factor of falling.<sup>8,9</sup> However, no significant decline in the fall risk in men with high cortisol levels was found. The opposite direction in women and men of the associations between serum total cortisol and recurrent falling may be explained by the difference in testosterone levels. The anabolic effects of testosterone may counteract the catabolic effects of cortisol. Many studies in sports medicine have shown that the testosterone/cortisol ratio rather than the testosterone or cortisol level alone is important for physical functioning.<sup>10,11</sup> and e.g. <sup>12,13</sup> Since testosterone levels are higher in men than in women,<sup>14</sup> this effect may be stronger in men.

**Table 1.** The relationship between serum cortisol and recurrent falling in older women and men in the Longitudinal Aging Study Amsterdam.

Women				Men		
	n (% events)	OR	CI	n (% events)	OR	CI
Serum total cortisol						
Q1	174 (28.7)	1.00		111 (22.5)	1.00	
Q2	148 (28.4)	0.67	0.39-1.15	134 (23.1)	1.25	0.70-2.24
Q3	130 (21.5)	0.56	0.32-0.99	160 (28.1)	1.24	0.69-2.24
Q4	127 (21.3)	0.49	0.28-0.87	157 (24.8)	1.34	0.74-2.44
Serum free cortisol						
Q1	220 (25.5)	1.00		62 (25.8)	1.00	
Q2	151 (27.8)	0.83	0.48-1.42	128 (23.4)	0.76	0.42-1.38
Q3	124 (25.0)	0.78	0.44-1.47	167 (25.1)	1.06	0.60-1.88
Q4	83 (20.5)	0.60	0.33-1.09	202 (25.7)	1.02	0.56-1.84

The Odds Ratios (OR) and 95 % Confidence Intervals (CI) are presented after adjustment for age, alcohol use, BMI, fear of falling and physical activity. The lowest quartile is the reference category.

In the literature, two theories are described to explain the role of cortisol in health during aging. First, the fetal programming theory (also known as the Barker hypothesis) postulates that 'a baby's nourishment before birth and during infancy, as manifest in patterns of fetal and infant growth, programs the development of risk factors such as raised blood pressure and glucose intolerance'.<sup>15</sup> As a consequence of malnourishment, experienced as stress, the threshold for cortisol production will be decreased leading to higher basal levels of cortisol throughout the lifespan. Associations have been found between cortisol and age-related diseases such as diabetes mellitus and cardiovascular diseases.<sup>16,17</sup> The second theory is the Allostatic load model.<sup>18</sup> Allostasis is the ability of the body to adapt to environmental stress, i.e. inflammation or psychological stress.<sup>19</sup> Rapid activation of the allostatic system is necessary for successful coping with a stressor and rapid inhibition of the system is important for recovery.<sup>20</sup> Over activation or insufficient inhibition leads to sustained high levels of cortisol and may result in health problems.<sup>18,20</sup> High allostatic load scores (i.e. unbeneficial levels of 10 biological makers (range 0-10) including high cortisol level) have been associated with cardiovascular diseases, decreased physical functioning and functional decline.<sup>17,21</sup> These two theories may be complementary: environmental factors set the thresholds for cortisol production in early life and thus the body's ability to cope with stress during life. Ineffective coping strategies may lead to increased levels of cortisol throughout the lifespan and consequently chronic diseases, poor physical functioning, and falling in later life.

The associations found in *Chapter 4* between cortisol and diabetes mellitus (DM) and chronic non-specific lung disease (CNSLD) can be interpreted within the context of these theories. In line with the literature, high basal levels of cortisol were associated with an increased risk of DM. Remarkably, high basal levels of cortisol were associated with a decreased risk of CNSLD. The protective effect of cortisol on CNSLD may be explained by the anti-inflammatory effect of corticosteroids as used in the treatment of asthma and chronic obstructive pulmonary disease.<sup>22,23</sup>

Cortisol may have a different role in acute and chronic disease stages. In acute stages, such as inflammation and cardiac arrest, high levels of cortisol may be an adequate response for coping and recovery.<sup>24</sup> Cortisol stimulates whole body protein breakdown to gain amino acids necessary for the recovery process.<sup>25</sup> In chronic stages, cortisol levels should return within the normal range. Prolonged high levels of cortisol may lead to ongoing protein catabolism and consequently negative health outcomes such as DM and poor physical functioning. Contrastingly, studies on mortality risk in severe sepsis patients have shown that high levels of cortisol were associated with an increased mortality risk.<sup>26-28</sup> These discordant findings may be explained by concomitant changes in other hormones.<sup>25</sup>

### Prevention of falling in older persons with a high risk of recurrent falling

Worldwide, public health authorities stimulate physical activity among all age groups. However, among older persons, it has been hypothesized that both low and high levels of physical activity may be associated with an increased risk of falling. If this is true, falling may be an adverse effect of the public health policies to increase physical activity. In *Chapter 5* we falsified this hypothesis: the association between physical activity and (recurrent) falling was not U-shaped. The risk of recurrent falling decreased with increasing levels of physical activity. The shape of the association was similar in physically poor and well functioning older persons. The practical implications of these findings are that clinicians and public health authorities should continue stimulating physical activity among older persons, also in more frail older persons.

To select persons who may benefit from preventive interventions, fall risk profiles can be used. Several risk profiles to identify community-dwelling older persons at high risk of falling have been developed,<sup>8,29-33</sup> however, the accuracy of these profiles differs in populations with different characteristics. Therefore, evaluation of risk profiles in the population that presents itself after a fall is necessary to assess its validity in this group.<sup>34</sup> The fall risk profile developed in LASA consists of nine easy to measure items that predict the risk of recurrent falling.<sup>30</sup> We evaluated how accurate this profile predicts the risk of recurrent falling in a new sample of older persons who consulted the Emergency department or family physician after a fall. An important measure for the accuracy of a prediction model is the Area Under the Receiver Operator Curve (AUC), which is a measure for the discriminative ability. The AUC was 0.65 (CI: 0.58-0.72), indicating that 65 % of the randomly selected pairs of recurrent fallers and non-recurrent fallers are correctly classified as high and low risk of recurrent falling, respectively (*Chapter 7*). The optimal cut-off value was 8, however, for use in clinical practice, a lower cut-off value may be more appropriate to minimize misclassification of recurrent fallers. It was concluded that in a group of older persons seeking care after a fall, the LASA fall risk profile only moderately discriminates occasional fallers from recurrent fallers.

To our knowledge, only one other study evaluated the predictive validity of a fall risk profile in a group of older persons consulting the Emergency department after a fall. The FROP-com is a risk profile that predicts the risk of falling.<sup>33</sup> The AUC of the FROP-com was 0.65. The most important predictor of recurrent falling is having a history of falling. If this item alone is used to predict recurrent falling, an AUC of 0.64 is obtained. Thus, among older persons seeking care after a fall, other items of the risk profiles barely add to the discriminative ability of the item “two or more falls in the preceding year” when predicting who will fall again.

Over the past decades, many studies have evaluated multifactorial fall prevention programs.<sup>35-43</sup> Despite conflicting results, meta-analyses seem to favour multifactorial interventions.<sup>44-46</sup>

Multidisciplinary evaluation and treatment of fall risk factors is believed to be the best treatment available to reduce the number of falls in older persons and internationally, this approach is recommended in guidelines.<sup>47,48</sup> The effectiveness may be improved by restricting this approach to persons with the highest fall risk.<sup>49</sup> We conducted a randomised controlled trial with an economic evaluation to test this hypothesis (*Chapter 6*). After one year of follow-up, the time to first and time to second fall in participants who received the multidisciplinary evaluation and treatment of fall risk factors did not differ from those who received usual care (*Chapter 8*). Thus, the prevention program did not lower the risk of falling in persons with a high risk of recurrent falling. In addition, the intervention did not improve the level of daily functioning, physical functioning or quality of life.

In the fall prevention trial, we aimed to select participants at high risk of recurrent falling using the LASA fall risk profile. We wanted to select a high-risk group and therefore chose a relatively high cut-off value with a high specificity to ensure that the participants assigned to the high risk group would contain few misclassified non-recurrent fallers. Table 2 in *Chapter 7* shows that, at the cut-off value of 8, a high specificity of 80 % was obtained. Moreover, the proportion of recurrent fallers within one year of follow-up was 28 % in the usual care group, which is considerably higher than the proportions of recurrent fallers reported in general older populations (6-15 %).<sup>50-52</sup> This indicates that we did indeed select a group at high risk of recurrent falling.

As stated above, the effectiveness of fall prevention programs may be higher in persons with a high risk of falling.<sup>49</sup> The current findings provide evidence against this hypothesis. Lack of difference in (recurrent) fall incidences between the intervention and usual care group may be explained in several ways. First, the high-risk group may have been too frail. The component of the multifactorial approach for which most evidence is available that it lowers the fall risk is strength and balance exercise.<sup>44</sup> However, one study found that an exercise program reduced the fall risk in pre-frail older persons but increased the fall risk in frail older persons.<sup>53</sup> In line with this study, we found that among high-risk persons, those who did take part in exercise therapy had a higher fall risk than those who did not. Second, the adverse effect of exercise in this trial may have concealed the effectiveness of the other recommendations. However, when we repeated the analyses after adjustment for physiotherapy, no significant differences in time to first and second fall were found ( $HR \approx 1$ ,  $p > 0.60$ ). Third, not all recommendations have been adhered to. The adherence rate was 71 % for exercise, 78 % for medication and 40 % for other recommendations. These rates are within the ranges reported in other trials (exercise: 60-75 %, medication: 50 % and other recommendations: 50-75 %).<sup>36,38,40,54,55</sup> The adherence rates do not seem to be higher in positive than in negative trials. Fourth, the contrast between the intervention and control group may not have been clear enough. The intervention was based



on the guideline “Prevention of fall incidents in older persons”.<sup>48</sup> Since the Dutch Institute for Healthcare Improvement (CBO) released this guideline in 2004, the awareness of the burden of falling in older persons has gradually increased among primary care physicians. Maybe also control subjects have received evaluation and subsequent treatment of fall risk factors. Although the number of consultations was higher in the intervention group than in the usual care group (family physician: 735 vs. 647,  $p=0.27$ ; other physicians: 374 vs. 265,  $p=0.001$ ; physical- and occupational therapists: 2761 vs. 2129,  $p=0.04$ ), a surprisingly high number of participants in the usual care group consulted at least once a physician (74 %) or physical- or occupational therapist (66 %). Lack of contrast between the two groups cannot be ruled out.

Although the intervention did not reduce the fall risk, it may still reduce the costs in this group. If the intervention improves bone quality, muscle strength, and coping skills, the consequences of falls may be less severe and thus, the costs made after a fall may be lower. To test this, the differences in falls and utilities were compared with the difference in costs between in the intervention and usual care groups. The costs in the intervention group were somewhat, but not significantly, higher as compared with usual care (*Chapter 9*). The intervention was not superior to usual care. Since these findings are in line with a similar study conducted in Maastricht,<sup>56</sup> it was concluded that the multidisciplinary evaluation and treatment of fall risk factors should not be implemented among older persons with a high fall risk in the Netherlands.

### **Recommendations for future research and clinical practice**

The results in *Chapters 2, 3 and 4* have implications for future research. Replication of the analyses in a different sample is necessary to confirm the associations between cortisol and muscle mass and muscle strength. This replication study should be done in a larger sample to allow stratification for the glucocorticoid receptor gene polymorphisms. Sample size estimation suggests that over 4800 participants should be included. Given the diurnal pattern and the sensitivity to stress and nutrition, the time of measurement will affect the result to a great extent. The most precise cortisol assessment would be 24-hour measurement of serum levels. This measurement enables the analyses of the basal and peak level as well as the diurnal pattern and the HPA response to stimuli. However, this is not feasible in large cohort studies. In this type of study, late evening and waking salivary cortisol are reliable alternatives for the basal and peak levels, respectively. To confirm the hypothesized causal relationship between cortisol and muscle mass and muscle strength, large longitudinal studies are needed.

Recently, the effectiveness of multifactorial interventions to decrease the fall risk has been put forward for discussion: should researchers and clinicians continue to improve the concept of multifactorial strategies, or should we put this concept aside and focus on single strategies that have been proven effective?<sup>57</sup> This discussion should be held for unselected and high-risk

populations separately. In high-risk groups, ten different trials have studied the effectiveness of the multifactorial approach.<sup>36-39,42,54,58-60</sup> In these trials, high risk was mostly defined as having had at least one fall (recently or in the preceding year). Four studies that were done in the UK, US, and Australia reported a decline in fall incidence.<sup>37,42,54,58</sup> Two of the six studies in which the multifactorial approach did not reduce the fall incidence, were done in the Netherlands. Thus, especially in the Netherlands, multifactorial evaluation and treatment of fall risk factors does not reduce the fall incidence in high-risk persons.

The effectiveness of the multifactorial approach in unselected populations has been evaluated in many trials and three meta-analyses. Two of the meta-analyses reported a significant decrease in fall rate,<sup>44,46</sup> whereas one did not.<sup>45</sup> The latter study included more trials. However, in a sub analyses, this latter study showed that trials with higher intensity interventions did reduce the fall rate (RR=0.84, CI: 0.74-0.96).<sup>45</sup> The multifactorial approach may reduce the fall risk only if direct treatment is provided instead of referrals, and if all caregivers are well trained and stick to the protocol.<sup>57</sup> The effectiveness in unselected populations may be improved if its multidisciplinary character is expanded and patients receive more supervision in realizing the recommendations. For instance, if pharmacists and (in)formal caregivers are notified, the adherence may be further improved. However, this will further increase the costs of the intervention and further research is needed addressing the cost-effectiveness in unselected populations, especially given the high number needed to treat (NNT). At least 10 persons need to be treated to prevent one fall.<sup>44,61</sup> Single interventions may be less expensive, although only few single interventions are supported with sufficient evidence. Interventions for which at least some evidence is available are strength and balance exercise,<sup>44,49,62</sup> withdrawal of psychotropic medication,<sup>63,64</sup> administration of vitamin D and calcium,<sup>65</sup> home hazard modification,<sup>46,66,67</sup> and managing fear of falling.<sup>68,69</sup> However, the estimated numbers needed to treat are even higher than for multifactorial interventions (NNT for exercise $\geq$ 16<sup>44,61</sup> and for vitamin D=15<sup>65</sup>) and will further increase when implemented in usual care. Finally, those multifactorial trials that did reduce the fall rate, were conducted in the US and UK.<sup>58,70,71</sup> Due to differences in health care policies, usual care in the Netherlands differs from these countries: for example, the health insurances and municipalities provide aids and adaptations such as walking aids, shower seats, and platform scooters. Nevertheless, the fall rate is similarly high. The effectiveness of multifactorial trials in unselected populations in the Netherlands has not been studied yet. In conclusion, there are some options for improvement of the multifactorial fall prevention strategy in unselected populations. Given the high number needed to treat it is important to further evaluate the cost-effectiveness of prevention programs in unselected populations, especially in the Netherlands.

In a group of older persons seeking care after a fall, the LASA fall risk profile only moderately discriminates occasional fallers from recurrent fallers. However, prediction of fall risk is only

relevant if an effective intervention is available to reduce the fall risk. The current evidence suggests that multifactorial interventions do not reduce the fall risk among high-risk persons. Both health care professionals and researchers should investigate new and different preventive strategies. In high-risk persons, non-modifiable risk factors may be more important, such as chronic diseases or previous falls. Although the burden of falling is the highest in this group, little evidence for effective strategies is available. Since the most important predictor for recurrent falling is a history of falling, primary prevention of falling is important. If the multifactorial approach can be optimized in unselected populations, the overall fall risk may be reduced and fewer persons may develop a high risk of recurrent falling. However, given the rise in number of older persons, it does not seem feasible to treat every older person and therefore the question remains: who should we treat?

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